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Complete List of Authors:	Ho, Iris Szu-Szu; The University of Edinburgh Usher Institute of Population Health Sciences and Informatics Azcoaga-Lorenzo, Amaya; University of St Andrews Bute Medical School Akbari, Ashley; Swansea University Medical School Davies, Jim; University of Oxford, Department of Computer Science Hodgins, Peter; The University of Edinburgh Usher Institute of Population Health Sciences and Informatics Khunti, Kamlesh; University of Leicester College of Life Sciences Kadam , Umesh ; University of Leicester College of Life Sciences Lyons, Ronan; Swansea University, Health Data Research UK McCowan, Colin ; University of St Andrews, School of Medicine Mercer, Stewart; The University of Edinburgh, Usher Institute Nirantharakumar, Krishnarajah; University of Birmingham Guthrie, Bruce; University of Edinburgh
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Variation in the estimated prevalence of multimorbidity: systematic review and meta-analysis of 194 international studies

Iris Szu-Szu Ho,[1] Amaya Azcoaga-Lorenzo,[2] Ashley Akbari,[3] Professor Jim Davies,[4] Peter Hodgins,[1] Kamlesh Khunti,[5] Umesh Kadam,[5] Ronan A Lyons,[3] Colin McCowan,[2] Stewart W Mercer,[1] Krishnarajah Nirantharakumar,[6] Bruce Guthrie.[1]

1. University of Edinburgh, Usher Institute, Medical School, Teviot Place, Edinburgh, EH8 9AG, United Kingdom
2. University of St Andrews, School of Medicine, Medical and Biological Sciences, North Haugh, St Andrews, KY16 9TF, United Kingdom
3. Swansea University, Medical School, Population Health Science, Singleton Park, Swansea, SA2 8PP, United Kingdom
4. University of Oxford, Department of Computer Science, Wolfson Building, Parks Road, Oxford, OX1 3QD, United Kingdom
5. University of Leicester, Leicester General Hospital, Gwendolen Road, Leicester, LE5 4PW, United Kingdom
6. University of Birmingham, Institute of Applied Health Research, Birmingham, B15 2TT, United Kingdom

Corresponding author: Iris Szu-Szu Ho. Email: iris.s.ho@outlook.com

Abstract

Objective. To examine the variation in the estimated prevalence of multimorbidity.

Methods. In this systematic review and meta-analysis, we conducted searches in nine bibliographic databases (PsycINFO, Embase, Global Health, Medline, Scopus, Web of Science, Cochrane Library, CINAHL, and ProQuest Dissertations & Theses Global) for prevalence studies published between database inception and 21 January 2020. Studies reporting the prevalence of multimorbidity (in all age groups and in community, primary care, care home and hospital settings) were included. Studies with an index condition or those that did not include people with no long-term conditions in the denominator were excluded. Retrieved studies were independently reviewed by two reviewers, and relevant data were extracted using pre-designed pro-forma. We used meta-analysis to pool the estimated prevalence of multimorbidity across studies, and used random-effects meta-regression and subgroup analysis to examine the association of heterogeneous prevalence estimates with study and measure characteristics.

Results. 13,807 titles were screened, of which 194 met inclusion criteria for meta-analysis. The pooled prevalence of multimorbidity was 42.7% (95%CI=39.2%-46.2%) with high heterogeneity (I^2>99%). In adjusted meta-regression models, participant mean age and the number of conditions included in a measure accounted for 52.6% of heterogeneity in effect sizes. The estimated prevalence of multimorbidity was significantly higher in studies with older adults and those that included larger numbers of conditions. There was no significant difference in estimated prevalence between low- or middle-income countries (37.8%) and high-income countries (44.3%), or between self-report (40.0%) and administrative/clinical databases (52.7%).

Conclusions. The pooled prevalence of multimorbidity was significantly higher in older populations and when studies included a larger number of baseline conditions. The findings suggest that, to improve study comparability and quality of reporting, future studies should use a common core conditions set for multimorbidity measurement and report multimorbidity prevalence stratified by socio-demographics.

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Strengths and limitations of this study

- This study used meta-regression to examine the variation of estimated prevalence of multimorbidity and how measure and study characteristics influenced prevalence estimates.
- The use of multiple imputation in this study minimised biased estimates caused by missing values and unbalanced classes and enhanced statistical accuracy.
- The inclusion of studies with various measure and study characteristics enabled a better understanding of the contributing factors of the heterogeneity of multimorbidity prevalence.
- Due to inconsistent reporting of multimorbidity prevalence and data unavailability, the estimated multimorbidity prevalence stratified by sex, ethnicity and socio-economic status could not be explored in this study.

Introduction

Population ageing is a worldwide phenomenon, with the World Health Organization (WHO, 2018) estimating that the proportion of the global population aged 60 and older will double from 12% to 22% between 2015 and 2050 [1]. A key implication of population ageing is that increasing numbers of people will be living with multimorbidity. Multimorbidity, commonly defined as the co-occurrence of two or more long-term conditions [2], adversely affects people's risk of death, health-related quality of life, functional ability, and mental well-being [3, 4]. Multimorbdiity affects all groups of society, but is known to be more common in older people, in women, and in those from low socio-economic backgrounds [5-7]. It poses major challenges to the delivery of care in health systems internationally which are often focused on the management of single diseases and lack appropriate coordination and continuity of care across different sectors [8, 9]. Disparities in health and health and social care could be found at any stage along the continuum of chronic diseases, from prevention to the management of diseases. To understand these disparities among multimorbid populations requires consistently monitoring the populations (e.g. incidence, prevalence, health impact, risk factors and delivery of care) defined by race and ethnicity, gender, age, socio-economic status, physical environment and geographic factors.

Previous systematic reviews have identified issues in the measurement of multimorbidity, related to the choice of chronic conditions counted in measures, the categorisation of conditions and diseases, and the counting or weighting method used [10, 11]. Although weighted measures are often used when the purpose of measurement is to predict future outcomes, a simple count of conditions remains the most commonly-used method for the measurement of multimorbidity, and is optimal for estimating multimorbidity prevalence [12]. However, the estimated prevalence of multimorbidity varies widely in the literature ranging from 3.5% to 100% [13], likely reflecting a combination of varying measures and varying populations studied [14]. This review aimed to examine variation in the estimated prevalence of multimorbidity, including estimated prevalence in different subgroups and associations with study and multimorbidity measure characteristics.

Methods

The systematic review and meta-analysis reported here is part of a larger review which aimed to examine 1) how multimorbidity has been constructed and 2) measured by international studies

(n=566) and 3) variation in the estimated prevalence of multimorbidity across studies. Analysis in relation to the first two registered objectives has been reported [15], and this paper reports the third registered objective.

Inclusion and exclusion criteria

The eligibility criteria for this review were defined based on the CoCoPop framework—Condition, Context, and Population [16]. The condition included in this review is prevalence of multimorbidity. The majority of studies defined multimorbidity as the co-existence of two or more chronic conditions, and used the cut-off to estimate its prevalence in a population of interest. We therefore included studies that used this definition for examining multimorbidity prevalence across international studies. For this analysis, we included studies carried out in the community, primary care, care home and hospitals, and those estimating the prevalence of multimorbidity in the population studied. Studies that did not include a relevant denominator population – for example, only examining patients with an index condition or excluding patients who did not have multimorbidity – were excluded. Qualitative research, studies not published in English, and conference abstracts were also excluded.

Search strategy

The search strategy for this review was developed in collaboration with a specialist medical librarian (Supplementary Table S1). Key terms relevant to multimorbidity and measurement were combined using Boolean logic to identify studies that met the inclusion criteria. We included medical subject headings to provide a sensitive search for relevant literature. Databases included in the search were Ovid interface (PsycINFO, Embase, Global Health, Medline), Scopus, Web of Science, Cochrane Library, EBSCO interface (CINAHL Plus), and ProQuest Dissertations & Theses Global, from inception to 21 January 2020. In addition to the database searches, our secondary search strategy included hand-searching reference lists of retrieved articles and tracked citations to maximise the yield.

Study screening and selection

Articles retrieved from databases were organised using EndNote X9 bibliographic software and Excel, and then were imported to Covidence for screening [17]. Titles, abstracts, and full-texts of retrieved articles were screened against the eligibility criteria by two reviewers. Throughout the review process, any disagreement that arose was resolved through discussion between the two

reviewers (IS-SH and PH), and through the involvement of a third reviewer (BG) if necessary. The study selection process is summarised in Figure 1.

Data extraction

We extracted data on the characteristics of the included studies using pre-designed data extraction pro-forma. The extracted data include 1) authors, 2) publication year, 3) study purpose, 4) method, 5) country, 6), continent, 7) country income (classified as 'high' and 'low or medium' [combined because of small numbers] allocated based on the World Bank Group at the time of review [18]), 8) study participants, 9) mean age, 10) sample size, 11) number of conditions, 12) setting, 13) data collection method/data source, 14) number of multimorbidity cases, and 15) proportion of multimorbidity (calculated based on item 10 and 14). Data on the estimated prevalence stratified by sex, ethnicity and socio-economic status were fragmented and unavailable in many studies, and thus these could not be retrieved for analyses.

Risk of bias assessment

We used the Effective Public Health Practice Project (EPHPP) quality assessment tool for quantitative studies to assess the risk of bias and the quality of each of the included studies, in terms of 1) selection bias, 2) study design, 3) confounders, 4) blinding, 5) data collection method, 6) withdrawals and dropouts [19]. We assessed also publication bias (rated high if there was selective reporting within studies) and conflict of interest (rated unclear if conflict of interest declaration was not reported). Each study was rated and assigned an overall risk of bias as 'high', 'moderate', or 'low' (please see the details in appendix p26).

Data analysis

We used descriptive statistics to measure frequency distribution, central tendency and variability of all variables. Univariate generalized linear models were used to investigate the association between continuous/count predictor (mean age/number of conditions) and categorical predictors We summarised the prevalence of multimorbidity using metaprop [20, 21]. The presence of effect size heterogeneity was examined using the Q statistic and I-squared. Significant heterogeneity was identified, so we used subgroup analysis and meta-regression with random-effects models to identify potential moderating factors.

Outlying studies were identified using studentised residuals, leave-one-out analysis and Mahalanobis distance. Studies with studentised residuals that were larger than 2 or 3 and those that contributed to heterogeneity in leave-one-out analyses were scrutinized [22]. Mahalanobis distance was used for pattern recognition and multivariate outlier detection [23]. Study effect sizes were graphically displayed to identify outlying studies and explore subgroup effects (Supplementary Figure S1). In initial analysis of heterogeneity and outliers, 24 studies were found to make a significant contribution to the high level of observed heterogeneity in multimorbidity prevalence and significant changes in the summary effect size. The 24 studies were excluded for one or more of the following reasons: 1) their contribution to high levels of heterogeneity in the leave-one-out test, 2) being identified as an outlying value in the studentised residuals test (z-score ≥ 2), 3) their Mahalanobis distance exceeding the chi-squared critical value at a 0.01 significance level, 4) infrequent values in compositional categorical data (e.g. only one study examined prevalence in children). The process of identifying outliers, the rationale for exclusion of each study, and the characteristics of outlying studies are documented in Supplementary Figure S2 and Table S2 and S3. Sensitivity analysis was performed to explore the impact of excluding the 24 studies in meta-analysis.

There was missingness in two predictors, with 37% missingness in the 'mean age' of the study population variable (some of which reported it categorically, and thus were treated as missing data) and 6% missingness in the 'number of conditions' included in the multimorbidity measure variable. Multiple imputation with 60 imputed datasets and 10 iterations was performed where random forest was used to impute missing data [24, 25]. Following multiple imputation, fraction of missing information (FMI) was computed to quantify the impact of missing data, which ranged from 0.05 to 0.3 indicating that the uncertainty in the values imputed for missing data is small/moderate [26].

A random-effects regression tree approach with ten-fold cross-validation was used to identify subgroups (cut-offs) of the 'mean age' and 'number of conditions' variables with differential effect sizes [27]. Given considerable variation in the effect sizes, we conducted meta-regression with the restricted maximum likelihood (REML) estimator to examine the possible sources of heterogeneity in effect sizes [20, 21, 28]. As the variable 'multimorbidity prevalence' did not follow the normal distribution (positively skewed), we applied logit transformation to the variable for analyses and converted the logits back to odds ratios (e^{logit}) and proportions ($p=e^{logit}/e^{logit}+1$) for reporting. For model selection, we refitted the models using maximum likelihood and then

conducted a log-likelihood test to compare the fit of models [29]. A permutation test with 1000 permuted datasets was performed on the final meta-regression model to calculate p value and avoid type 1 error [30]. Subgroup analysis with the REML method was used to estimate the pooled multimorbidity prevalence of subgroups of each variable (age, the number of conditions included in a measure, setting, data source, continent, country income, study risk of bias). Forest-like plots were used to display the effect sizes of included studies [31]. The presence of publication bias was assessed using Egger's test, which did not find evidence of publication bias [32]. All statistical tests were performed using R version 4.0.4.

Patients and public involvement

No patients were involved in the development of the research question, outcome measures, study design and implementation. Nonetheless, we have previously discussed preliminary review findings and issues relevant to multimorbidity measurement with our patient and public involvement group. We plan to disseminate the review findings to researchers, clinicians, policy makers and public audiences through news media, social media and seminars.

Results

After screening 13,807 titles and abstracts, 218 studies were identified which estimated the prevalence of multimorbidity using a cut-off of 'two or more' conditions. Following the removal of 24 outlying studies, 194 studies were included in the meta-analysis (Table 1, Supplementary Table S4). Of the 194 studies, 64 studies were from Europe, 47 from North America, 45 from Asia, 11 from Australasia, 12 from South America, and four from Africa (Table 1 and Figure

2). Seventy-four percent of studies were from high-income countries (n=145) and 25.3% from low- and middle-income countries (LMICs) (one from low-income, nine from lower middle-income, 29 from upper middle-income, and 10 from multiple low- and middle-income countries). The majority of studies (n=147) estimated the prevalence of multimorbidity in community settings, followed by primary care (n=33) and hospital setting (n=14). Prevalence data were collected through either self-report (n=151) or medical records and administrative databases (n=43). In a univariate linear regression (Supplementary Table S5), we found that studies from Europe, database studies and studies conducted in hospital settings were more likely to measure multimorbidity in an older population and included a larger number of conditions in a

multimorbidity measure, compared to those from other continents, self-report studies, and studies conducted in primary care and community settings. In respect to risk of bias in included studies (Supplementary Table S6 and Figure S3), 11.3% were rated as high risk of bias, 84% as moderate risk of bias, and 4.6% as low risk of bias.

The pooled estimate of multimorbidity prevalence across the 194 studies was 42.7% (95%CI 39.2%-46.2%), τ^2 is 1.0 (95%CI 0.9-1.3) with high heterogeneity (I^2>99%), and meta-regression was therefore used to examine study characteristics associated with heterogeneity. Mean age (F=103.1, p<0.0001, R^2=34.7%) and number of conditions (F=34.4, p<0.0001, R^2=14.8%) were the strongest univariate predictors and positively associated with the estimated prevalence of multimorbidity (Figure 3). Meta-regression tree analysis (Supplementary Figure S4) partitioned the mean age variable into three homogeneous subgroups (aged <59, aged 59-73, aged ≥74) and the number of conditions variable into four homogeneous subgroups (<9, 9-19, 20-43, ≥44). The categorical 'mean age' and 'number of conditions' variables explained 42.7% and 17.3% of the heterogeneity in effect sizes respectively (larger than the original numerical variables). We therefore used the categorical variables identified from the regression trees for meta-analyses.

In univariate meta-regression, primary care studies (pooled multimorbidity prevalence 49.7%, OR 1.5, 95%CI 1.0-2.2) and hospital based studies (pooled multimorbidity prevalence 59.6%, OR 2.2, 95%CI 1.3-3.9) had significantly higher rates of multimorbidity than community-based studies (39.5%) (Table 2). Multimorbidity prevalence was significantly higher in database studies (pooled multimorbidity prevalence 52.7%, OR 1.7, 95%CI 1.2-2.4) than self-report studies (pooled multimorbidity prevalence 40.0%). In the mean age categorical variable, the pooled prevalence estimates of the three subgroups were statistically significantly different from one another, and considerably higher in studies with mean participant age ≥74 (pooled multimorbidity prevalence 69.0%, OR 5.7, 95%CI 4.2-7.7) and mean participant age 59-73 (pooled multimorbidity prevalence 50.3%, OR 2.6, 95%CI 2.0-3.3) than those with mean participant age <59 (pooled multimorbidity prevalence 28.2%) (Table 2 and Figure 4). Similar patterns were also found in the number of conditions variable where studies including ≥44 conditions in measurement (pooled multimorbidity prevalence 87.6%, OR 15.0, 95%CI 5.9-38.3), 20-43 conditions (pooled multimorbidity prevalence 51.4%, OR 2.2, 95%CI 1.5-3.3), and 9-19 conditions (pooled multimorbidity prevalence 43.2%, OR 1.6, 95%CI 1.2-2.2) yielded higher prevalence estimates than studies including <9 conditions in measurement (pooled multimorbidity prevalence 32.1%)

with a dose-response relationship. The estimated prevalence of multimorbidity was 44.3% in high-income countries compared to 37.8% in low or middle income countries, but the difference was not statistically significantly different (OR 1.3, 95%CI 0.9-1.8). In study risk of bias, no statistically significant difference in pooled prevalence of multimorbidity was found between studies with low, moderate and high risk of bias.

In the adjusted meta-regression model, we found that compared to studies where participant mean age was <59, multimorbidity prevalence remained significantly higher in studies with mean participant age 59-73 (OR 2.5, 95%CI 2.0-3.1) and in studies with mean participant age ≥74 (OR 4.7, 95%CI 3.6-6.2). Compared to measures including <9 conditions, multimorbidity prevalence was higher in measures including ≥44 conditions (OR 7.3, 95%CI 3.5-15.0), 20-43 conditions (OR 2.1, 95%CI 1.5-2.8), and 9-19 conditions (OR 1.6, 95%CI 1.3-2.0). Nonetheless, no difference was found between primary care, community, and hospital settings. Compared to studies from North America, prevalence was lower in studies from Europe (OR 0.6, 95%CI 0.4-0.7), Australasia (OR 0.6, 95%CI 0.4-0.9), or Asia (OR 0.6, 95%CI 0.4-0.7). No significant difference in prevalence estimates between self-report and routine database studies was evident after controlling for study and measure characteristics. The model explained 56.8% of the heterogeneity in multimorbidity prevalence, with the mean age and number of conditions variables providing most explanatory power (52.6% of the heterogeneity).

Sensitivity analysis including the 24 outlying studies (Supplementary Table S7) was similar to primary analysis except for "study setting" variable. The mean participant age and number of conditions variables remained the strongest predictors of multimorbidity prevalence in sensitivity analysis. However, the estimated prevalence in sensitivity analysis (including outlying studies) was much lower in studies including ≥44 conditions in a multimorbidity measure (pooled multimorbidity prevalence 51.6, OR 2.5, 95%CI 1.5-4.0) compared to primary analysis excluding outlying studies (pooled multimorbidity prevalence 87.6, OR 7.3, 95%CI 3.5-15.0). The difference in estimates was mainly attributed to the three outlying studies that included 146, 147 and 259 conditions in a measure respectively but yielded relatively low mean multimorbidity prevalence (mean prevalence 54.3%)[33-35]. In respect to study settings, the pooled prevalence in sensitivity analysis was statistically significantly higher in primary care compared to community in both unadjusted and adjusted models, whereas in primary analysis the difference was not statistically significant after controlling for study and measure characteristics. The higher pooled prevalence

in primary care settings found in sensitivity analysis could be explained by two outlying primary care based studies that had mean participant age of 56 but high estimated prevalence (89.1% and 72.7% respectively) [34, 36].

Discussion

The overall estimate of multimorbidity prevalence in adults across all the included studies was 42.7% (95%CI=39.2%-46.2%), but with very high heterogeneity. More than half of the observed heterogeneity was explained by study mean participant age and the number of conditions included in the multimorbidity measure, with older age and larger number of conditions strongly associated with a higher prevalence of multimorbidity. The difference in estimated prevalence was small between self-report and administrative/clinical databases, and between study settings. No significant difference was found between studies from low- or middle-income and high-income countries, but North American studies had higher estimated prevalence than other continents.

Two prior systematic reviews examined the prevalence of multimorbidity across studies [37, 38]. Fortin et al. (2012) conducted a narrative review of 21 studies and found various operationalisations of multimorbidity and a large variation in the prevalence of multimorbidity, particularly in studies with participants aged 75 and older [37]. Nguyen et al. (2019) meta-analysed the prevalence of multimorbidity across 70 studies from community settings and found that the pooled estimated prevalence was 33.1% with high levels of heterogeneity (I^2 >99%) [38]. The pooled prevalence of multimorbidity in Nguyen et al study is lower than in this study, likely because we have included studies from primary care and hospital settings (the pooled prevalence of multimorbidity in community-based studies in this analysis was 39.5%). Nguyen et al. (2019) did not carry out a meta-regression, but in narrative analysis comment that the prevalence of multimorbidity appeared higher in older adults and women [38]. Our review findings are consistent with previous literature finding that age is most important determinant of multimorbidity [5, 37-39]. While we did not find a significant difference between low and middle-income and high-income countries, Nguyen et al. in their review showed a statistically significantly higher pooled prevalence in high-income countries (the pooled prevalence from 18 studies was 37%) than low or middle-income countries (the pooled prevalence from 31 studies was 29%). This difference in findings may be due to the inclusion in our review of a larger number of studies from high-income or upper middle-income countries, whereas very few studies were from low-income or lower

middle-income countries. The low number of included studies from low-income countries in this review could be explained by fewer attention paid to this relatively new research field (multimorbidity) in low-income countries and our literature search restricted to English language (proficient language of reviewers). The estimated prevalence of multimorbidity in North America was higher compared to other continents in this study despite older study populations and larger numbers of conditions found in studies from Europe. Possible explanation of the results could be related to over-diagnosis and medicalisation [40].

The strengths of this review are searches conducted in multiple databases, the large number of studies identified and the use of meta-analytic approaches to examine factors associated with heterogeneity of estimated multimorbidity prevalence. We examined and handled outlying studies and missing data (multiple imputation) with rigour and excluded studies that did not take into account 'healthy' populations (populations with no long-term conditions) to minimize biased estimates of multimorbidity prevalence. This review has limitations. Sensitivity analysis including all studies had similar findings with two exceptions, namely that sensitivity analysis found: a weaker (but still statistically significant) association with the number of conditions included in the multimorbidity measure than primary analysis; and a statistically significantly higher pooled prevalence in primary care compared to community based studies versus no significant association in primary analysis. Although we examined associations with study characteristics including mean participant age, a limitation is the lack of information in the reviewed studies on prevalence estimates stratified by participant characteristics including sex, ethnicity, and socio-economic status. An additional uncontrolled factor is how studies measured multimorbidity in terms of the type (as opposed to the number) of the conditions included in measures, which varied substantially across studies with too much heterogeneity to model [15]. Last but not least, measurement of multimorbidity is a relatively new research field and its labelling has been used variably. Thus, it is likely that not all relevant studies were identified and included in this review, but we were rigorous in our application of inclusion/exclusion criteria and did not favour adding known papers that did not appear in the search or where excluded through the process.

In spite of the methodological limitations, this review adds to our understanding of how study and measure characteristics can influence the estimated prevalence of multimorbidity. Mean age of the study population and the number of conditions included in the multimorbidity measure were the major factors associated with varying estimated prevalence of multimorbidity. A key implication

is that comparing prevalence between studies requires more stratified estimates of multimorbidity prevalence. We therefore strongly recommend that as well as overall prevalence, future studies should clearly report multimorbidity prevalence stratified by age and sex at a minimum, and ideally by ethnicity and socio-economic status. This will allow readers to capture a more holistic picture of multimorbidity prevalence in the population studied, and allow better comparison of prevalence in different populations, and accurate pooled estimates of prevalence in reviews.

Additionally, the number of conditions included in a measure is strongly associated with estimated multimorbidity prevalence. It would be ideal if studies additionally reported prevalence using a common core set of conditions agreed by consensus. Parallel reporting of the bespoke set chosen for the context and purpose, and a core set would improve comparability of prevalence estimates, and help identify the additional value of any bespoke multimorbidity measures. The lack of any significant difference in estimated prevalence between self-report and clinical/administrative databases in this review suggests that provided careful attention is paid to the number and type of conditions included in measures, exactly how data is collected may be less important.

To conclude, in recent years, there has been an increasing interest in the epidemiology of multimorbidity internationally. This review finds that population characteristics and measurement content are the major factors that influenced prevalence estimates of multimorbidity. Studies with older populations and larger numbers of conditions yielded a higher estimate of multimorbidity prevalence. However, heterogeneity between studies has made comparison of multimorbidity prevalence across studies difficult. To improve comparability and quality of reporting, this review suggests that future studies should use common core condition set for the measurement of multimorbidity and clearly report the prevalence of multimorbidity stratified by socio-demographics.

Contributorship statement

All authors have made substantial contributions: CMC, KN, UK, KK, RAL, JD, AA, AAL and SWM were involved in conception of the work, acquisition of funding, and critically commenting on the manuscript. IS-SH led and BG substantially contributed to the design, analysis, and interpretation of data for the review, and are responsible for the decision to submit the manuscript. IS-SH and PH screened and reviewed retrieved studies. All authors contributed to the edits of the manuscript and had access to the data. The final draft has been approved by all authors.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: we had financial support from HDRUK for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Data sharing statement

Study data are available in supplementary appendix.

Figure legends

Figure 1: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram

Figure 2: Country of origin of the included studies estimating the prevalence of multimorbidity (except studies from multiple countries)

Figure 3: Relationship between the prevalence of multimorbidity and mean age or number of conditions (the area of points is proportional to inverse variances)

Figure 4: The distribution of prevalence estimates within the subgroups of mean age and number of conditions (forest-like plot for a large review**)**

Table 1: Summary of study characteristics (Supplementary Table S8 shows the definition of variables)

Name of variable	Descriptive statistics (n=194)
Prevalence of multimorbidity (%)	Range: 5.4 to 95.6 Median: 38.4 (IQR 28.3 to 57.0) Mean: 43.5 (SD 20.7) Pooled prevalence with the REML estimator: 42.7 (39.2-46.2)
Mean age of study population (year)	Range: 32.2-83.8 Median: 62.4 (IQR 49.9 to 72.3) Mean: 61.1 (SD 12.8)
No of conditions (count)	Range: 3-75 Median: 14 (IQR 9 to 20) Mean: 17 (SD 10)
Country income (count, %)	
High income	145 (74.7%)
Low- or Middle-income	49 (25.3%)
Continent (count, %)	
Europe	64 (33.0%)
North America	47 (24.2%)
Asia	45 (23.2%)
Australasia	11 (5.7%)
South America	12 (6.2%)
Africa	4 (2.1%)
Multiple continents	11 (5.7%)
Study population (count, %)	
Only older people	63 (32.5%)
Middle-aged and older	46 (23.7%)
All adults	85 (43.8%)
Setting (count, %)	
Community	147 (75.8%)
Primary care	33 (17.0%)
Hospital	14 (7.2%)
Source (count, %)	
Self-report	151 (77.8%)
Database	43 (22.2%)
Risk of bias assessment (count, %)	
Low	9 (4.6%)
Moderate	163 (84.0%)
High	22 (11.3%)

IQR: Interquartile range. SD: Standard deviation. The percentages were rounded so they do not add to 100%.

Table 2: Output of meta-analytic models (n=194)

	Pooled prevalence of multimorbidity of each subgroup (%, 95% CI)	Meta-regression Unadjusted Odds Ratio (95% CI)	Meta-regression Adjusted Odds Ratio (95% CI) R^2 56.8%	FMI
Group of mean age		R^2 42.7%		
<59	28.2 (25.4-31.2)	Ref	Ref	Ref
59-73	50.3 (45.3-55.3)	2.6 (2.0-3.3)***	2.5 (2.0-3.1)***	0.3
≥74	69.0 (62.9-74.5)	5.7 (4.2-7.7)***	4.7 (3.6-6.2)***	0.2
No of conditions		R^2 17.3%		
<9	32.1 (27.3-37.2)	Ref	Ref	Ref
9-19	43.2 (38.9-47.7)	1.6 (1.2-2.2)**	1.6 (1.3-2.0)***	0.2
20-43	51.4 (42.9-59.7)	2.2 (1.5-3.3)***	2.1 (1.5-2.8)***	0.2
≥44	87.6 (81.3-92.0)	15.0 (5.9-38.3)***	7.3 (3.5-15.0)***	0.05
Setting		R^2 4.8%		
Community	39.5 (36.1-43.1)	Ref	Ref	Ref
Primary care	49.7 (39.1-60.4)	1.5 (1.0-2.2)*	1.2 (0.9-1.7)	0.1
Hospital	59.6 (45.6-72.2)	2.2 (1.3-3.9)**	1.2 (0.7-1.8)	0.2
Source		R^2 3.9%		
Self-report	40.0 (36.2-43.8)	Ref	Ref	Ref
Database	52.7 (45.2-60.1)	1.7 (1.2-2.4)**	0.9 (0.7-1.3)	0.2
Continent		R^2 4.1%		
North America	50.4 (43.6-57.3)	Ref	Ref	Ref
Europe	44.8 (38.2-51.5)	0.8 (0.5-1.2)	0.6 (0.4-0.7)***	0.2
Australasia	35.8 (29.5-42.5)	0.5 (0.3-1.0)**	0.6 (0.4-0.9)**	0.07
Asia	35.3 (29.3-50.0)	0.5 (0.4-0.8)*	0.6 (0.4-0.7)***	0.1
South America	47.5 (31.2-64.4)	0.9 (0.5-1.7)	0.8 (0.5-1.3)	0.1
Africa	23.6 (16.3-32.8)	0.3 (0.1-0.8)	0.6 (0.3-1.1)	0.2
Multiple continents	38.4 (29.1-48.6)	0.6 (0.3-1.2)	0.7 (0.4-1.1)	0.1
Country income		R^2 0.8%		
Low or middle-income	37.8 (31.4-44.7)	Ref		
High-income	44.3 (40.3-48.4)	1.3 (0.9-1.8)		
Study risk of bias		R^2 0.0%		
Low risk	33.3 (20.2-49.6)	Ref		
Moderate risk	42.7 (39.1-46.4)	1.5 (0.8-2.9)		
High risk	46.4 (34.1-59.1)	1.7 (0.8-3.8)		
Publication year		1.0 (1.0-1.0)		

*<0.05 **<0.01 ***<0.001

Ref: Reference category. FMI: Fraction of missing information

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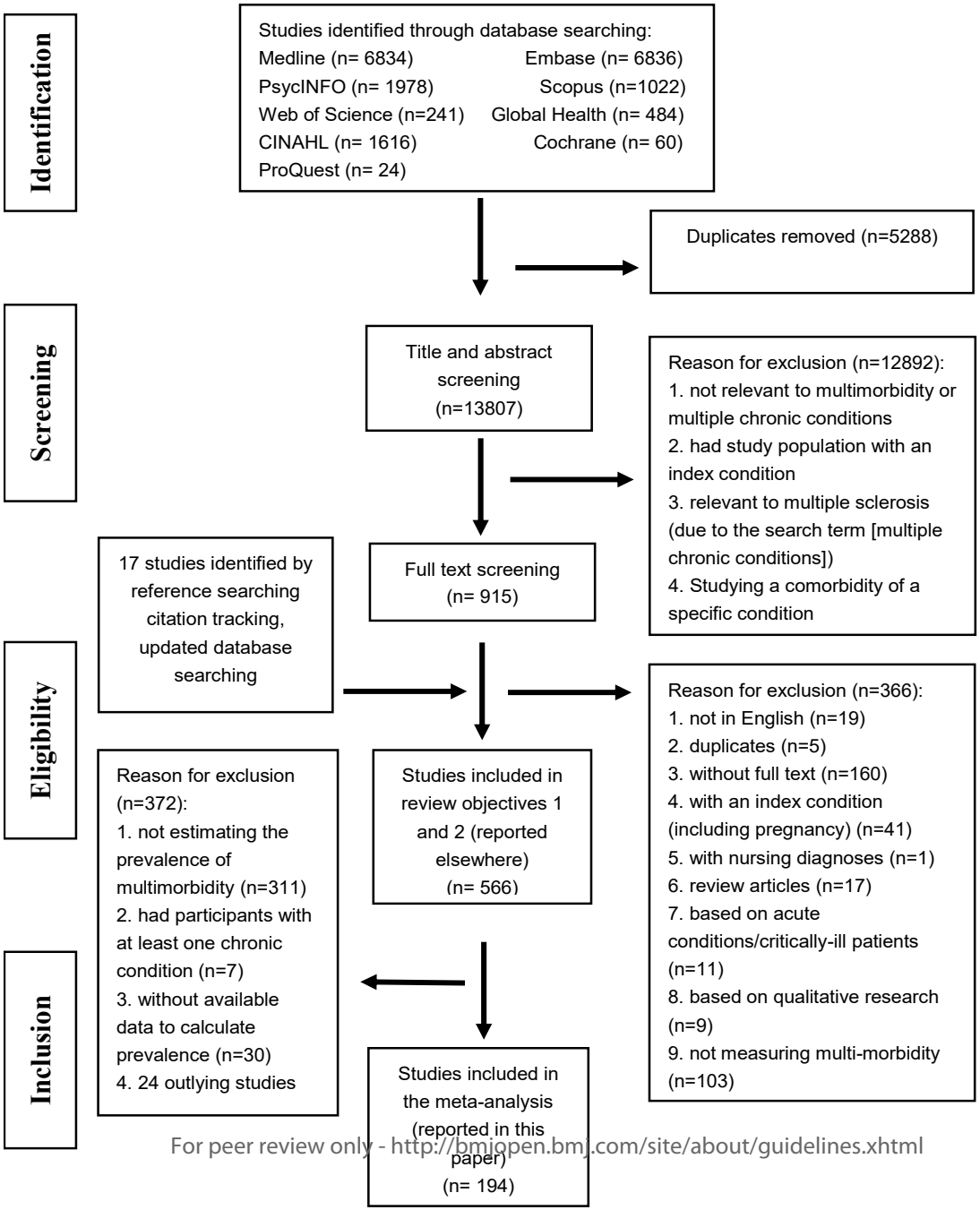

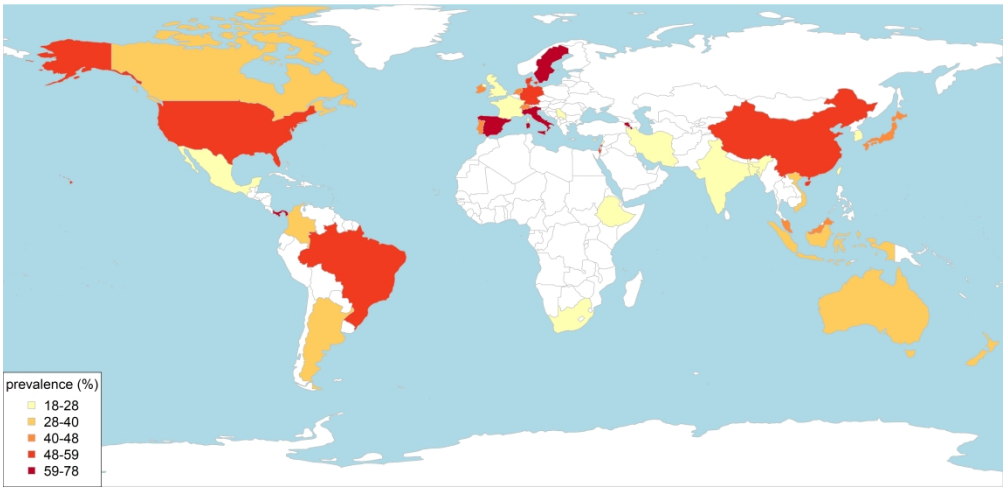

Figure 2: Country of origin of the included studies estimating the prevalence of multimorbidity (except studies from multiple countries)

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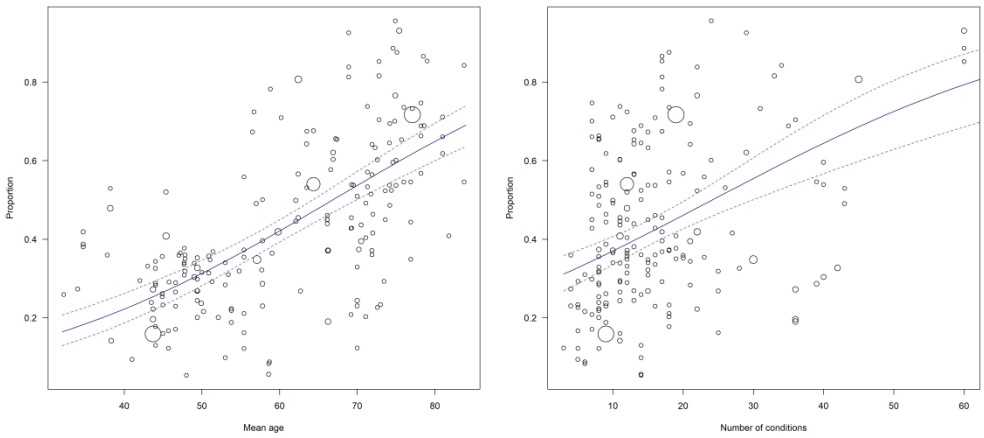

Figure 3: Relationship between the prevalence of multimorbidity and mean age or number of conditions (the area of points is proportional to inverse variances)

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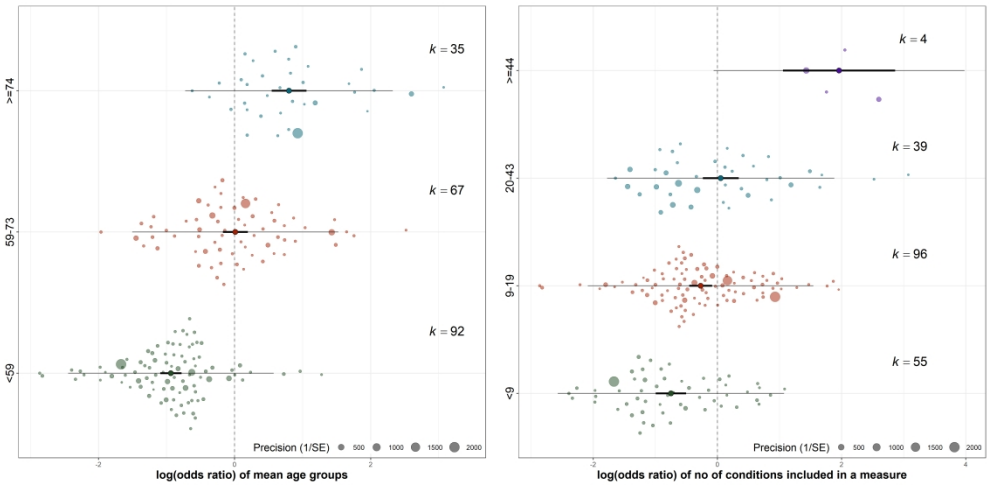

Figure 4: The distribution of prevalence estimates within the subgroups of mean age and number of conditions (forest-like plot for a large review)

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Supplementary appendix

Supplement to: Ho ISS, Azcoaga-Lorenzo A, Akbari A, et al. Variation in the estimated prevalence of multimorbidty: systematic review and meta-analysis of 194 studies.

Table of Contents

Table S1: Search strategy

Database	Search strategy
Ovid Interface PsycINFO Embase Global Health Ovid MEDLINE	1. (multimorbidit$ or multi-morbidit$ or comorbidit$ or co-morbidit$ or polymorbidit$ or poly-morbidit$ or multicondition$ or multicondition$ or "multiple chronic condition$" or "morbidity burden" or ((multiple or coexisting or co-existing or concurrent or con-current or comorbid or co-morbid) adj2 (disease$ or illness$ or condition$ or diagnos$ or morbid$))).m_titl. 2. (measure$ or index or indices or instrument$ or scale$ or "disease count$").mp. 3. 1 and 2 4. Limit 3 to human
EBSCO Interface CINAHL Plus	1. MM (multimorbidit* or multi-morbidit* or comorbidit* or co-morbidit* or polymorbidit* or poly-morbidit* or multicondition* or multicondition* or "multiple chronic condition*" or "morbidity burden" or ((multiple or coexisting or co-existing or concurrent or con-current or comorbid or co-morbid) N2 (disease* or illness* or condition* or diagnos* or morbid*))) 2. AB (measure* or index or indices or instrument* or scale*) 3. 1 AND 2 Limiters – Full Text; Human; Language: English
Scopus	TITLE (multimorbidit* or multi-morbidit* or comorbidit* or co-morbidit* or polymorbidit* or poly-morbidit* or multicondition* or multicondition* or "multiple chronic condition*" or "morbidity burden" or ((multiple or coexisting or co-existing or concurrent or con-current or morbid or co-morbid) W/2 (disease* or illness* or condition* or diagnos?s or morbid*))) AND TITLE (measure* or index or indices or instrument* or scale* or "disease counts")
Web of Science	(TI=(measure* or index or indices or instrument* or scale*))AND (TI=(multimorbidit* or multi-morbidit* or comorbidit* or co-morbidit* or polymorbidit* or poly-morbidit* or multicondition* or multicondition* or 'multiple chronic condition*' or 'morbidity burden' or ((multiple or coexisting or co-existing or concurrent or con-current or comorbid or co-morbid) NEAR/2 (disease* or illness* or condition* or diagnos* or morbid*)))) AND LANGUAGE: (English)
Cochrane library	(multimorbidity or multi-morbidity or comorbidity or co-morbidity or polymorbidity or poly-morbidity or multicondition or multicondition or 'multiple chronic conditions' or 'morbidity burden' or ((multiple or coexisting or co-existing or concurrent or con-current or comorbid or co-morbid) NEAR/2 (disease or illness or condition or diagnosis or morbid))) AND (measure or index or indices or instrument or scale or "disease count*"):ti
ProQuest Dissertations & Theses Global	ti((multimorbidit* OR multi-morbidit* OR comorbidit* OR co-morbidit* OR polymorbidit* OR poly-morbidit* OR multicondition* OR multicondition* OR 'multiple chronic condition*' OR 'morbidity burden' OR ((multiple OR coexisting OR co-existing OR concurrent OR con-current OR morbid OR co-morbid) NEAR/2 (disease* OR illness* OR condition* OR diagnos?s OR morbid*)))) AND noft((measure* OR index OR indices OR instrument* OR scale*)) Limited by: Manuscript type: Doctoral dissertations, Master's theses Language: English

Table S2: Summary of outlying studies

Name of variable	Outlying studies (n=24)
Prevalence of multimorbidity (%)	Range: 7.3 to 89.1 Median: 28.1 (IQR 14.6 to 48.7) Mean: 34.3 (SD 23.5)
Mean age of study population (year)	Range: 39.6 to 82.2 Median: 56.6 (IQR 52.3 to 66.4) Mean: 59.3 (SD 11.5)
No of conditions (count)	Range: 7 to 259 Median: 34 (IQR 19 to 54) Mean: 52 (SD 58)
Country income (count, %)	
High income	21 (87.5%)
Low- or Middle-income	3 (11.5%)
Continent (count, %)	
Europe	6 (25.0%)
North America	7 (29.2%)
Asia	7 (29.2%)
Australasia	3 (12.5%)
Multiple continents	1 (4.2%)
Study population (count, %)	
Only older people	2 (8.3%)
Middle-aged and older	1 (4.2%)
All adults	15 (62.5%)
Only children	1 (4.2%)
All age population	5 (20.8%)
Setting (count, %)	
Community	12 (50.0%)
Primary care	7 (29.2%)
Hospital	4 (16.7%)
Care home	1 (4.2%)
Source (count, %)	
Self-report	8 (33.3%)
Database	16 (66.6%)
Risk of bias assessment (count, %)	
Low	4 (16.7%)
Moderate	19 (79.2%)
High	1 (4.2%)

IQR: Interquartile range. SD: Standard deviation. The percentages were rounded so they do not add up to 100%.

Table S3: Characteristics of 24 outlying studies

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias	Rationale for exclusion
[1] Stanley et al (2018)	New Zealand	Australasia	High	Hospitals	All adults	Not reported	3489747	Medical records and administrative database	61	275706	0.08	Moderate	Contributing to high levels of heterogeneity of effect sizes (Leave-one-out analysis) and the studentized residual of this study is more than 2 standard deviations away from its expected value.
[2] Lenzi et al (2016)	Italy	Europe	High	Hospitals	All adults	66.4	3759836	Medical records and administrative database	26	574208	0.15	Moderate	Contributing to high levels of heterogeneity of effect sizes (Leave-one-out analysis)
[3] Hu et al (2019)	Taiwan	Asia	High	Community	All adults	Not reported	1429527	Medical records and administrative database	20	939485	0.66	Low	Contributing to high levels of heterogeneity of effect sizes (Leave-one-out analysis)
[4] Gawron et al (2020)	USA	North America	High	Hospitals	All adults but not older people	Not reported	741612	Medical records and administrative database	Not reported	53824	0.07	Moderate	Contributing to high levels of heterogeneity of effect sizes (Leave-one-out analysis) and the studentized residual of this study is more than 2 standard deviations away from its expected value.
[5] Low et al (2019)	Singapore	Asia	High	Community	All adults	39.6	1181024	Self-report	48	309428	0.26	Low	Contributing to high levels of heterogeneity of effect sizes (Leave-one-out analysis)
[6] Wang et al (2014)	China	Asia	Low or middle	Community	Whole population	Not reported	162464	Self-report	40	17987	0.11	Low	Contributing to high levels of heterogeneity of effect sizes (Leave-one-out analysis)
[7] Gaulin et al (2019)	Canada	North America	High	Hospitals	All adults	51.2	1316832	Medical records and administrative database	34	416282	0.32	Moderate	Contributing to high levels of heterogeneity of effect sizes (Leave-one-out analysis)

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias	Rationale for exclusion
[8] Violan et al (2014)	Spain	Europe	High	Primary care	All adults	47.4	1356761	Medical records and administrative database	146	645818	0.48	Moderate	Contributing to high levels of heterogeneity of effect sizes (Leave-one-out analysis)
[9] Nicholson et al (2019)	Canada	North America	High	Primary care	All adults	52.3	367743	Medical records and administrative database	20	195838	0.53	High	Contributing to high levels of heterogeneity of effect sizes (Leave-one-out analysis)
[10] Bao et al (2019)	China	Asia	Low or middle	Community	Middle aged and older	61.36	18137	Self-report	19	3773	0.21	Moderate	Contributing to high levels of heterogeneity of effect sizes (Leave-one-out analysis)
[11] Fortin et al (2005)	Canada	North America	High	Primary care	All adults	56.55	980	Medical records and administrative database	14	873	0.89	Moderate	The studentized residual of this study is more than 2 standard deviations away from its expected value.
[12] Prazeres et al (2015)	Portugal	Europe	High	Primary care	All adults	56.3	1993	Medical records and administrative database	147	1449	0.73	Moderate	Its Mahalanobis distance exceeds the chi-squared critical value at a 0.01 significance level (multivariate outlier detection)
[13] Lawson et al (2013)	UK	Europe	High	Community	All adults	72.7	7054	Medical records and administrative database	40	1243	0.18	Moderate	Irregular patterns found in compositional data (in scatter plot and Mahalanobis distance test)- low prevalence in studies with high mean participant age and a larger number of conditions
[14] Sullivan et al (2012)	USA	North America	High	Community	All adults	Not reported	47178	Medical records and administrative database	259	19666	0.42	Moderate	Its Mahalanobis distance exceeds the chi-squared critical value at a 0.01 significance level (multivariate outlier detection)

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias	Rationale for exclusion
[15] Peng et al (2020)	China	Asia	Low or middle	Community	Only older people	71.6	1321	Self-report	15	589	0.45	Moderate	Contributing to high levels of heterogeneity of effect sizes (in leave-one-out analysis)
[16] Excoffier et al (2018)	Switzerland	Europe	High	Primary care	All adults	56.5	2904	Medical records and administrative database	75	1513	0.52	Moderate	Its Mahalanobis distance exceeds the chi-squared critical value at a 0.01 significance level (multivariate outlier detection)
[17] Chung et al (2015)	Hong Kong	Asia	High	Community	All adults	Not reported	25780	Self-report	46	3227	0.13	Moderate	Its Mahalanobis distance exceeds the chi-squared critical value at a 0.01 significance level (multivariate outlier detection)
[18] Ki et al (2017)	South Korea	Asia	High	Community	All adults	57.05	19942	Medical records and administrative database	66	5979	0.30	Moderate	Its Mahalanobis distance exceeds the chi-squared critical value at a 0.01 significance level (multivariate outlier detection)
[19] Bobo et al (2016)	USA	North America	High	Community	Whole population	Not reported	138858	Self-report	19	33682	0.24	Moderate	Infrequent values in compositional categorical data (few studies focused on whole population)
[20] Randall et al (2018)	Australia	Australasia	High	Community	Whole population	Not reported	5437018	Self-report	30	660449	0.12	Moderate	Infrequent values in compositional categorical data (few studies focused on whole population)
[21] Russell et al (2020)	New Zealand	Australasia	High	Community	Only children	Not reported	3838	Self-report	7	374	0.10	Moderate	Infrequent values in compositional categorical data (only one study focused on children population)
[22] Barnett et al (2012)	UK	Europe	High	Primary care	Whole population	Not reported	1751841	Medical records and administrative database	40	406427	0.23	Low	Infrequent values in compositional categorical data (few studies focused on whole population)

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias	Rationale for exclusion
[23] St Sauver et al (2015)	USA	North America	High	Primary care	Whole population	Not reported	106061	Medical records and administrative database	20	34592	0.33	Moderate	Infrequent values in compositional categorical data (few studies focused on whole population)
[24] Vetrano et al (2016)	Denmark, Finland, Iceland, Italy, the Netherlands, Norway, United Kingdom, Czech Republic, France, Sweden and Germany, Canada	Multiple continents	High	Care homes	Only older people	82.2	6903	Medical records and administrative database	13	5098	0.74	Moderate	Infrequent values in compositional categorical data (only one study focused on care home)

MM: Multimorbidity. No of participants: The total number of participants in the denominator for estimating prevalence in a study (which could be a subset in some included studies)

Table S4: Characteristics of 194 included studies

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[25] Aarts et al (2012)	The Netherlands	Europe	High	Primary care	All adults	55.4	1184	Medical records and administrative database	23	420	0.35	Moderate
[26] Aarts et al (2011a)	The Netherlands	Europe	High	Community	Middle aged and older	70	15188	Self-report	Not reported	7729	0.51	Moderate
[27] Aarts et al (2011b)	The Netherlands	Europe	High	Primary care	All adults	55.4	1763	Medical records and administrative database	23	985	0.56	Moderate
[28] Abizanda et al (2014)	Spain	Europe	High	Primary care	Only older people	78.6	842	Medical records and administrative database	14	580	0.69	Moderate
[29] Agborsangaya et al (2012)	Canada	North America	High	Community	All adults	46.6	4003	Self-report	16	919	0.23	Moderate
[30] Agborsangaya et al (2013)	Canada	North America	High	Community	All adults	47.8	4803	Self-report	16	1729	0.36	Moderate
[31] Agborsangaya et al (2014)	Canada	North America	High	Community	All adults	47.7	4752	Self-report	16	1597	0.34	Moderate
[32] Ahrenfeldt et al (2019)	Europe	Europe	High	Community	Middle aged and older	66.25	244258	Self-report	10	90652	0.37	Moderate
[33] Alimohammadian et al (2017)	Iran	Asia	Low or middle	Community	Middle aged and older	Not reported	49946	Self-report	8	10035	0.20	Moderate
[34] Angst et al (2002)	Switzerland	Europe	High	Primary care	All adults	Not reported	591	Medical records and administrative database	10	201	0.34	High

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[35] Appa et al (2014)	USA	North America	High	Community	All adults	60.2	1997	Self-report	16	1417	0.71	Moderate
[36] Adams et al (2017)	USA	North America	High	Community	All adults	Not reported	400000	Self-report	12	191600	0.48	Moderate
[37] Ahmadi et al (2016)	Iran	Asia	Low or middle	Community	Middle aged and older	52.1	49946	Self-report	8	10035	0.20	Moderate
[38] Amaral et al (2018)	Brazil	South America	Low or middle	Community	Only older people	Not reported	264	Self-report	8	175	0.66	Moderate
[39] An et al (2016)	South Korea	Asia	High	Community	Middle aged and older	54.8	10118	Self-report	8	3228	0.32	Moderate
[40] Araujo et al (2018)	Brazil	South America	Low or middle	Community	All adults	Not reported	4001	Self-report	12	1160	0.29	Moderate
[41] Arnold-Reed et al (2018)	Australia	Australasia	High	Primary care	All adults	38.2	4285	Medical records and administrative database	43	2269	0.53	Moderate
[42] Arokiasamy et al (2015)	6 low middle income countries (China, Ghana, India, Mexico, Russia, South Africa)	Multiple continents	Low or middle	Community	All adults	Not reported	42236	Self-report	8	9250	0.22	Moderate
[43] Sinnige et al (2015)	The Netherlands	Europe	High	Primary care	Middle aged and older	66.9	120480	Medical records and administrative database	29	74733	0.62	Moderate
[44] Zemedikun et al (2018)	UK	Europe	High	Community	Middle aged and older	Median age 58	502643	Medical records and administrative database	36	95710	0.19	Moderate
[45] Wensing et al (2001)	The Netherlands	Europe	High	Primary care	All adults	Not reported	3867	Self-report	25	626	0.16	Moderate
[46] Mounce et al (2018)	UK	Europe	High	Community	Middle aged and older	Not reported	4564	Self-report	15	1553	0.34	Moderate
[47] Taylor et al (2010)	Australia	Australasia	High	Community	All adults	Not reported	3206	Self-report	7	547	0.17	Low

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[48] Vancampfort et al (2019)	Six low and middle income countries (China, Ghana, India, Mexico, Russia, and South Africa)	Multiple continents	Low or middle	Community	Middle aged and older	62.4	34129	Self-report	11	15529	0.46	Moderate
[49] Vancampfort et al (2018)	Six low and middle income countries (China, Ghana, India, Mexico, Russia, and South Africa)	Multiple continents	Low or middle	Community	Only older people	72.6	14585	Self-report	11	8780	0.60	Moderate
[50] Aubert et al (2016)	Switzerland	Europe	High	Primary care	Middle aged and older	63.5	1002	Medical records and administrative database	17	676	0.67	Moderate
[51] Autenrieth et al (2013)	Germany	Europe	High	Community	Only older people	75.7	1007	Self-report	13	658	0.65	Moderate
[52] Bahler et al (2015)	Switzerland	Europe	High	Community	Only older people	74.9	229493	Medical records and administrative database	22	175752	0.77	Moderate
[53] Vancampfort et al (2017)	44 low and middle income countries	Multiple continents	Low or middle	Community	All adults	38.3	194431	Self-report	11	27518	0.14	Moderate
[54] Banjare et al (2014)	India	Asia	Low or middle	Community	Only older people	Not reported	310	Self-report	20	176	0.57	Moderate
[55] Barra et al (2015)	USA	North America	High	Community	All adults	45.36	43079	Self-report	Not reported	22412	0.52	Moderate
[56] Bernard et al (2016)	Australia	Australasia	High	Hospitals	Only older people	81.8	306	Medical records and administrative database	19	125	0.41	High
[57] Biswas et al (2019)	Bangladesh	Asia	Low or middle	Community	All adults	Not reported	8763	Self-report	3	1078	0.12	Moderate

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[58] Blakemore et al (2016)	UK	Europe	High	Primary care	Only older people	75	4377	Self-report	24	2631	0.60	Moderate
[59] Blyth et al (2008)	Australia	Australasia	High	Community	Only older people	76.9	1685	Self-report	18	920	0.55	Moderate
[60] Bowling et al (2019)	USA	North America	High	Community	Middle aged and older	56.7	4217	Self-report	12	3053	0.72	Moderate
[61] Britt et al (2008)	Australia	Australasia	High	Primary care	All adults	Not reported	9156	Medical records and administrative database	18	3398	0.37	Moderate
[62] Broeiro-Goncalves et al (2019)	Portugal	Europe	High	Hospitals	All adults	59.8	800376	Medical records and administrative database	22	335357	0.42	Moderate
[63] Bruce et al (2010)	Canada	North America	High	Community	All adults	37.8	453	Self-report	4	163	0.36	High
[64] Burgers et al (2010)	France, Germany, Canada, Australia, Netherlands, New Zealand, UK, USA	Multiple continents	High	Community	All adults	Not reported	8973	Self-report	7	4037	0.45	Moderate
[65] Burke et al (2017)	US, Europe, Asia	Multiple continents	High	Community	Only older people	Not reported	4668	Self-report	9	2165	0.46	Moderate
[66] Buurman et al (2016)	The Netherlands	Europe	High	Hospitals	Only older people	78.2	639	Medical records and administrative database	35	440	0.69	Moderate
[67] Calderon-Larranaga et al (2017)	Sweden	Europe	High	Primary care	Only older people	74.6	3363	Self-report	60	2980	0.89	Moderate
[68] Camargo-Casas et al (2018)	Colombia	South America	Low or middle	Community	Only older people	71.1	2000	Self-report	12	808	0.40	Moderate

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[69] Canevelli et al (2019)	Italy	Europe	High	Primary care	Only older people	75.1	185	Medical records and administrative database	18	162	0.88	High
[70] Chamberlain et al (2020)	USA	North America	High	Community	All adults	Not reported	198941	Self-report	21	78527	0.39	Low
[71] Chen et al (2018)	China	Asia	Low or middle	Community	Only older people	Not reported	30774	Medical records and administrative database	33	25101	0.82	Low
[72] Chen et al (2018)	China	Asia	Low or middle	Community	Middle aged and older	Not reported	3737	Self-report	16	1722	0.46	Moderate
[73] Cheung et al (2013)	Hong Kong (SAR of China)	Asia	High	Community	Middle aged and older	71.3	1145	Self-report	18	654	0.57	Moderate
[74] Chu et al (2018)	Hong Kong (SAR of China)	Asia	High	Primary care	Middle aged and older	Not reported	382	Medical records and administrative database	40	206	0.54	Moderate
[75] Chudasama et al (2019)	UK	Europe	High	Community	Middle aged and older	Median age:58	491939	Medical records and administrative database	36	96622	0.20	Moderate
[76] Cimarras-Otal et al (2014)	Spain	Europe	High	Community	All adults	Not reported	22190	Self-report	20	7830	0.35	Moderate
[77] Chin et al (2016)	Hong Kong (SAR of China)	Asia	High	Primary care	All adults	Median age: 48	9259	Self-report	8	2350	0.25	Moderate
[78] Agrawal et al (2016)	India, China, Russia, Mexico, South Africa, Ghana	Multiple continents	Low or middle	Community	All adults	57.8	40166	Self-report	9	9238	0.23	Moderate
[79] Gu et al (2018)	China	Asia	Low or middle	Community	Only older people	Not reported	411	Self-report	13	232	0.56	Moderate
[80] Gunn et al (2012)	Australia	Australasia	High	Primary care	All adults	50.89	6864	Self-report	12	2154	0.31	Moderate

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[81] Han et al (2013)	USA	North America	High	Primary care	Only older people	76	159	Medical records and administrative database	18	117	0.74	High
[82] Hanlon et al (2018)	UK	Europe	High	Community	All adults	Not reported	493737	Medical records and administrative database	42	161576	0.33	Low
[83] Jantsch et al (2018)	Brazil	South America	Low or middle	Community	All adults	42	3092	Self-report	11	912	0.29	Moderate
[84] John et al (2003)	USA	North America	High	Community	Only older people	71.3	992	Self-report	11	732	0.74	High
[85] Johnson-Lawrence et al (2017)	USA	North America	High	Community	All adults	49.9	115097	Self-report	9	27278	0.24	Moderate
[86] Johnston et al (2019)	UK	Europe	High	Community	All adults	48	7184	Self-report	Not reported	388	0.05	Moderate
[87] Jones et al (2016)	USA	North America	High	Community	Only older people	Not reported	6964	Self-report	10	4951	0.71	Moderate
[88] Jovic et al (2016)	Serbia	Europe	Low or middle	Community	All adults	49.4	13103	Self-report	13	3522	0.27	Moderate
[89] Juul-Larsen et al (2020)	Denmark	Europe	High	Hospitals	Only older people	Median age: 78	369	Self-report	34	311	0.84	Moderate
[90] Hudon et al (2008)	Canada	North America	High	Community	All adults	Not reported	16782	Self-report	25	5343	0.32	Low
[91] Hussain et al (2015)	Indonesia	Asia	Low or middle	Community	Middle aged and older	Not reported	9438	Self-report	12	3369	0.36	Moderate
[92] Ie et al (2017)	USA	North America	High	Hospitals	Only older people	Not reported	1084	Medical records and administrative database	24	1036	0.96	High
[93] Ishizaki et al (2019)	Japan	Asia	High	Community	Only older people	76.9	2525	Self-report	9	1121	0.44	Moderate

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[94] Danon-Hersch et al (2012)	Switzerland	Europe	High	Community	Only older people	Not reported	1283	Self-report	12	448	0.35	Moderate
[95] de Heer et al (2013)	USA	North America	High	Community	All adults	47.72	1002	Self-report	19	378	0.38	Moderate
[96] Demirchyan et al (2013)	Armenia	Asia	Low or middle	Community	All adults	58.8	721	Self-report	Not reported	564	0.78	High
[97] Fabbri et al (2015)	Italy	Europe	High	Community	Only older people	73.6	1018	Self-report	15	458	0.45	Moderate
[98] Fillenbaum et al (2000)	USA	North America	High	Community	Only older people	73.44	4034	Self-report	5	1181	0.29	Moderate
[99] Kaneko et al (2019)	Japan	Asia	High	Community	Only older people	Not reported	253	Self-report	Not reported	135	0.53	Moderate
[100] Kang et al (2017)	South Korea	Asia	High	Primary care	All adults	32.2	590	Medical records and administrative database	14	153	0.26	Moderate
[101] Gandhi et al (2020)	USA	North America	High	Community	All adults	Not reported	9499	Self-report	8	3379	0.36	Moderate
[102] Costa et al (2018)	Brazil	South America	Low or middle	Community	Only older people	Not reported	1451	Self-report	29	1343	0.93	Moderate
[103] Rizzuto et al (2017)	Sweden	Europe	High	Community	Only older people	Not reported	1099	Self-report	36	774	0.70	Moderate
[104] Dhalwani et al (2017)	UK	Europe	High	Community	Middle aged and older	Not reported	5476	Self-report	18	1156	0.21	Moderate
[105] Elixhauser et al (1998)	USA	North America	High	Hospitals	All adults	57.1	1779167	Medical records and administrative database	30	619150	0.35	Low
[106] Fabbri et al (2015)	USA	North America	High	Hospitals	Only older people	72.3	695	Self-report	15	440	0.63	Moderate

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[107] Fortin et al (2014)	Canada	North America	High	Community	Middle aged and older	57.8	1196	Self-report	14	599	0.50	Moderate
[108] Fuchs et al (1998)	Israel	Asia	High	Community	Only older people	Not reported	1820	Self-report	14	1174	0.65	Moderate
[109] Galenkamp et al (2011)	The Netherlands	Europe	High	Community	Middle aged and older	69.2	2046	Self-report	7	876	0.43	High
[110] Galenkamp et al (2016)	Germany, UK, Italy, The Netherlands, Spain and Sweden	Europe	High	Community	Only older people	74.2	2792	Self-report	8	1358	0.49	Moderate
[111] Gamma et al (2001)	Switzerland	Europe	High	Community	All adults	Not reported	407	Self-report	14	53	0.13	High
[112] Ge et al (2018)	Singapore	Asia	High	Community	All adults	51.4	1940	Self-report	17	715	0.37	Moderate
[113] Ge et al (2019)	Singapore	Asia	High	Community	All adults	51.3	1932	Self-report	17	564	0.29	Moderate
[114] Gould et al (2016)	USA	North America	High	Community	Only older people	74.82	4184	Self-report	7	2932	0.70	Moderate
[115] Habib et al (2014)	Lebanon	Asia	Low or middle	Community	All adults	46.6	2501	Self-report	Not reported	665	0.27	Moderate
[116] Harrison et al (2017)	Australia	Australasia	High	Primary care	All adults	Not reported	8707	Medical records and administrative database	28	2838	0.33	Moderate
[117] Hayek et al (2017)	Israel	Asia	High	Community	All adults	47.2	4325	Self-report	10	1579	0.37	Moderate
[118] Henninger et al (2012)	USA	North America	High	Community	Only older people	76	3212	Self-report	9	1753	0.55	Moderate
[119] Hernandez et al (2019)	Ireland	Europe	High	Community	Middle aged and older	Not reported	6101	Self-report	31	4468	0.73	Moderate

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[120] Ho et al (2014)	Singapore	Asia	High	Community	Middle aged and older	66.15	1844	Self-report	12	830	0.45	Moderate
[121] Khan et al (2019)	Bangladesh	Asia	Low or middle	Community	All adults	58.6	12338	Self-report	6	1031	0.08	Low
[122] Kiliari et al (2013)	Cyprus	Europe	High	Community	All adults	53	465	Self-report	Not reported	132	0.28	Moderate
[123] King et al (2018)	USA	North America	High	Community	All adults	Not reported	5541	Self-report	11	3342	0.60	Moderate
[124] Kingston et al (2018)	UK	Europe	High	Community	All adults	Not reported	9723900	Self-report	12	5250906	0.54	High
[125] Koyanagi et al (2018)	China, Ghana, India, Mexico, Russia, and South Africa	Multiple continents	Low or middle	Community	Middle aged and older	62.1	32715	Self-report	10	16324	0.50	Moderate
[126] Kriegsman et al (2004)	The Netherlands	Europe	High	Community	Middle aged and older	69.2	2489	Self-report	7	519	0.21	Moderate
[127] Kristensen et al (2019)	Germany	Europe	High	Community	Middle aged and older	63.47	19605	Self-report	13	12600	0.64	Moderate
[128] Kristensen et al (2019)	Germany	Europe	High	Community	Middle aged and older	64.37	7604	Self-report	13	5140	0.68	Moderate
[129] Kunna et al (2017)	China, Ghana	Multiple continents	Low or middle	Community	Middle aged and older	Not reported	15864	Self-report	7	4731	0.30	Low
[130] Kuwornu et al (2014)	Canada	North America	High	Community	All adults	51.05	3284	Self-report	15	1143	0.35	Moderate
[131] Lai et al (2019)	Hong Kong (SAR of China)	Asia	High	Community	All adults	Not reported	69636	Self-report	14	3898	0.06	Moderate
[132] Lai et al (2018)	Hong Kong (SAR of China)	Asia	High	Community	All adults	Not reported	300	Self-report	11	48	0.16	Moderate
[133] Laires et al (2019)	Portugal	Europe	High	Community	All adults	Not reported	15196	Self-report	13	6671	0.44	Moderate

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[134] Lang et al (2015)	USA	North America	High	Community	Middle aged and older	53.4	3058	Self-report	6	948	0.31	Moderate
[135] Le Cossec et al (2016)	France	Europe	High	Community	Middle aged and older	70	15325	Self-report	4	3528	0.23	Moderate
[136] Lee et al (2007)	USA	North America	High	Hospitals	Middle aged and older	Not reported	741847	Medical records and administrative database	11	302792	0.41	Low
[137] Lee et al (2018)	Taiwan	Asia	High	Community	Only older people	Not reported	20898	Medical records and administrative database	Not reported	4234	0.20	High
[138] Li et al (2016)	UK	Europe	High	Primary care	All adults	Not reported	27806	Self-report	12	10332	0.37	Moderate
[139] Li et al (2019)	USA	North America	High	Community	Middle aged and older	67.4	14996	Self-report	8	9805	0.65	Moderate
[140] Lujic et al (2017)	Australia	Australasia	High	Community	Middle aged and older	70.2	90352	Self-report	8	33792	0.37	Moderate
[141] Lupianez-Villanueva et al (2018)	14 European countries	Europe	High	Community	All adults	Not reported	14000	Self-report	13	3416	0.24	Moderate
[142] Zhou et al (2018)	Bangladesh, India and China	Asia	Low or middle	Community	All adults	Not reported	18696	Self-report	9	3512	0.19	Moderate
[143] Zhang et al (2019)	China	Asia	Low or middle	Community	Only older people	70.5	11707	Self-report	11	5104	0.44	Moderate
[144] Wong et al (2010)	Canada	North America	High	Community	Only older people	Not reported	740	Self-report	7	489	0.66	Moderate
[145] Weimann et al (2016)	South Africa	Africa	Low or middle	Community	All adults	34	18526	Self-report	4	5057	0.27	Moderate
[146] Wang et al (2017)	Australia	Australasia	High	Community	All adults	44	8820	Self-report	8	2539	0.29	Moderate
[147] Wang et al (2019)	South Africa	Africa	Low or middle	Community	Only older people	Not reported	2627	Self-report	5	439	0.17	Moderate

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[148] Wade et al (2019)	New Zealand	Australasia	High	Community	All adults	59.05	7654	Self-report	12	2786	0.36	Moderate
[149] Maciejewski et al (2019)	USA	North America	High	Community	Only older people	77.1	20124230	Medical records and administrative database	19	14425446	0.72	Moderate
[150] Marengoni et al (2016)	Sweden	Europe	High	Community	Only older people	74.4	3155	Medical records and administrative database	14	1654	0.52	Moderate
[151] Marengoni et al (2009)	Sweden	Europe	High	Community	Only older people	Not reported	1099	Self-report	22	575	0.52	Moderate
[152] Marques et al (2018)	13 European countries	Europe	High	Community	All adults	50.2	32931	Self-report	6	7113	0.22	Moderate
[153] Mavaddat et al (2014)	UK	Europe	High	Primary care	Middle aged and older	58.7	11439	Self-report	6	1006	0.09	Moderate
[154] McDaid et al (2013)	Ireland	Europe	High	Community	Middle aged and older	Not reported	6018	Self-report	8	733	0.12	High
[155] Melis et al (2014)	Sweden	Europe	High	Hospitals	Only older people	83.75	390	Medical records and administrative database	39	213	0.55	Moderate
[156] Min et al (2007)	USA	North America	High	Community	Only older people	81	372	Self-report	9	230	0.62	High
[157] Momtaz et al (2010)	Malaysia	Asia	High	Community	Only older people	69.26	385	Self-report	16	165	0.43	Moderate
[158] Mondor et al (2018)	Canada	North America	High	Community	All adults	Not reported	27195	Medical records and administrative database	17	11390	0.42	Moderate
[159] Muggah et al (2012)	Canada	North America	High	Community	All adults	Not reported	28450000	Medical records and administrative database	9	4523550	0.16	Moderate
[160] Nagel et al (2008)	Germany	Europe	High	Community	Middle aged and older	56.5	13781	Self-report	15	9275	0.67	Moderate

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[161] Niedzwiedz et al (2019)	USA	North America	High	Community	Middle aged and older	67.2	2272	Self-report	8	1491	0.66	Moderate
[162] Nunes et al (2016)	Brazil	South America	Low or middle	Community	All adults	45.75	2927	Self-report	11	852	0.29	Moderate
[163] Nunes et al (2017)	Brazil	South America	Low or middle	Community	All adults	43.7	60202	Self-report	22	13365	0.22	Moderate
[164] Nunes et al (2015)	Brazil	South America	Low or middle	Community	Only older people	Not reported	1593	Self-report	17	1295	0.81	Moderate
[165] Olaya et al (2017)	Spain	Europe	High	Community	Only older people	71.75	2113	Self-report	7	1088	0.51	Moderate
[166] Olivares et al (2017)	Argentina	South America	High	Community	All adults	43	1044	Self-report	Not reported	346	0.33	Moderate
[167] Park et al (2018)	South Korea	Asia	High	Community	Middle aged and older	62.7	5996	Self-report	25	1607	0.27	Moderate
[168] Patel et al (2006)	Mexico	South America	Low or middle	Community	Middle aged and older	73	7852	Self-report	5	1833	0.23	Moderate
[169] Pati et al (2016)	India	Asia	Low or middle	Community	All adults	44.96	103	Self-report	18	24	0.23	Moderate
[170] Pati et al (2019)	India	Asia	Low or middle	Primary care	All adults	44	1649	Self-report	21	567	0.34	Moderate
[171] Pati et al (2017)	India	Asia	Low or middle	Primary care	All adults	44	1649	Self-report	21	467	0.28	Moderate
[172] Payne et al (2013)	UK	Europe	High	Primary care	All adults	49	180815	Medical records and administrative database	40	54945	0.30	Moderate
[173] Perez et al (2020)	Sweden	Europe	High	Community	Only older people	72.8	2596	Self-report	60	2213	0.85	Moderate
[174] Petersen et al (2019)	South Africa	Africa	Low or middle	Primary care	All adults	Not reported	2549	Self-report	Not reported	893	0.35	Moderate

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[175] Pfortmueller et al (2013)	Switzerland	Europe	High	Hospitals	All adults	Median age: 28	3170	Medical records and administrative database	18	1183	0.37	High
[176] Pressley et al (1999)	USA	North America	High	Hospitals	Only older people	Not reported	5934	Medical records and administrative database	Not reported	3534	0.60	Moderate
[177] Prior et al (2016)	Denmark	Europe	High	Community	All adults	Not reported	118410	Self-report	39	33937	0.29	Moderate
[178] Ribeiro et al (2018)	Brazil	South America	High	Community	Only older people	70	820	Self-report	8	270	0.33	Moderate
[179] Ruel et al (2014)	Australia	Australasia	High	Community	All adults	50	1854	Self-report	8	585	0.32	Moderate
[180] Ruel et al (2014)	China	Asia	Lor or middle	Community	All adults	49	1020	Self-report	11	346	0.34	Moderate
[181] Ryan et al (2018)	Ireland	Europe	High	Community	Middle aged and older	Not reported	4823	Self-report	16	2588	0.54	Moderate
[182] Schmidt et al (2016)	Austria, Belgium, Denmark, France, Germany, Italy, the Netherlands, Spain, Sweden, and Switzerland	Europe	High	Community	Only older people	Not reported	56609	Self-report	11	13794	0.24	Moderate
[183] Schottker et al (2016)	Germany	Europe	High	Primary care	Middle aged and older	Median age:70	2547	Medical records and administrative database	14	251	0.10	Moderate
[184] Seo et al (2017)	South Korea	Asia	High	Community	Middle aged and older	Not reported	156747	Self-report	15	42006	0.27	Moderate
[185] She et al (2019)	China	Asia	Low or middle	Hospitals	Only older people	68.9	1497	Self-report	22	1255	0.84	Moderate
[186] Singh et al (2019)	India	Asia	Low or middle	Community	All adults	41	16287	Self-report	5	1531	0.09	Moderate

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[187] Stepanova et al (2015)	USA	North America	High	Community	All adults	34.7	26225	Self-report	13	9992	0.38	High
[188] Stickley et al (2020)	USA	North America	High	Community	All adults	44.9	15311	Self-report	9	3996	0.26	High
[189] Streit et al (2014)	Switzerland	Europe	High	Primary care	Middle aged and older	63.5	1002	Medical records and administrative database	17	676	0.67	Moderate
[190] Stubbs et al (2018)	China, Ghana, India, Mexico, Russia, South Africa	Multiple continents	Low or middle	Community	Middle aged and older	62.4	34129	Self-report	13	19317	0.57	Moderate
[191] Su et al (2016)	China	Asia	Low or middle	Community	Only older people	Not reported	2058	Self-report	10	1012	0.49	Moderate
[192] Sundstrup et al (2017)	USA	North America	High	Community	All adults	43.5	10427	Self-report	8	2489	0.24	High
[193] Takahashi et al (2016)	USA	North America	High	Hospitals	All adults	57	6402	Medical records and administrative database	Not reported	3140	0.49	High
[194] Tinetti et al (2011)	USA	North America	High	Community	Only older people	72.6	5298	Self-report	5	1200	0.23	High
[195] Troelstra et al (2020)	The Netherlands	Europe	High	Community	All adults	Not reported	604	Self-report	26	321	0.53	High
[196] van Zon et al (2020)	USA	North America	High	Community	Middle aged and older	53.8	10719	Self-report	8	2390	0.22	Moderate
[197] Vancampfort et al (2017)	China, Ghana, India, Mexico, Russia, and South Africa	Multiple continents	Low or middle	Community	All adults	Median age: 62	32585	Self-report	11	14524	0.45	Moderate
[198] Vassilaki et al (2015)	USA	North America	High	Primary care	Only older people	78.5	2176	Medical records and administrative database	17	1884	0.87	Moderate
[199] Vassilaki et al (2016)	USA	North America	High	Primary care	Only older people	79	1449	Medical records and administrative database	17	1237	0.85	Moderate

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[200] Villarreal et al (2015)	Panama	South America	High	Primary care	Only older people	78.2	304	Self-report	7	227	0.75	Moderate
[201] Violan et al (2019)	Spain	Europe	High	Primary care	Only older people	75.4	916619	Medical records and administrative database	60	853085	0.93	Moderate
[202] von Strauss et al (2000)	Sweden	Europe	High	Community	Only older people	Not reported	502	Self-report	15	155	0.31	Moderate
[203] Vos et al (2013)	The Netherlands	Europe	High	Community	Only older people	71.9	315	Self-report	21	202	0.64	Moderate
[204] Vu et al (2019)	Vietnam	Asia	Low or middle	Hospitals	Only older people	71.9	405	Medical records and administrative database	Not reported	146	0.36	High
[205] Wang et al (2018)	USA	North America	High	Community	All adults	47	3086	Self-report	20	1109	0.36	Moderate
[206] Wang et al (2017)	China	Asia	Low or middle	Community	Only older people	69.24	2705	Self-report	17	1230	0.45	Moderate
[207] Wijers et al (2019)	Spain	Europe	High	Community	Middle aged and older	74.2	707	Self-report	21	491	0.69	Moderate
[208] Williams et al (2016)	USA	North America	High	Community	All adults	Not reported	23789	Self-report	9	9213	0.39	Moderate
[209] Woldesemayat et al (2018)	Ethiopia	Africa	Low or middle	Primary care	All adults	Not reported	411	Self-report	18	73	0.18	Moderate
[210] Yao et al (2020)	China	Asia	Low or middle	Community	Middle aged and older	57.7	10084	Self-report	15	3243	0.32	Moderate
[211] Yorke et al (2017)	USA	North America	High	Community	Middle aged and older	66.6	5877	Self-report	7	3391	0.58	Moderate
[212] You et al (2019)	China	Asia	Low or middle	Community	Only older people	72	5296	Self-report	27	2201	0.42	Moderate
[213] Zhang et al (2020)	China	Asia	Low or middle	Community	Only older people	74.14	4348	Self-report	15	2338	0.54	Moderate

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[214] Khanam et al (2011)	Bangladesh	Asia	Low or middle	Community	Only older people	69.5	452	Medical records and administrative database	9	243	0.54	Moderate
[215] Cornell et al (2009)	USA	North America	High	Primary care	All adults	62.4	1645314	Medical records and administrative database	45	1327382	0.81	Moderate
[216] Cassell et al (2018)	UK	Europe	High	Primary care	All adults	Not reported	403985	Medical records and administrative database	36	109884	0.27	Moderate
[217] Wong et al (2019)	Hong Kong (SAR of China)	Asia	High	Community	All adults	45.67	1014	Self-report	5	124	0.12	Moderate
[218] Puth et al (2017)	Germany	Europe	High	Community	All adults	Not reported	19294	Self-report	17	7640	0.40	Moderate

MM: Multimorbidity. No of participants is the total number of participants in the denominator for estimating prevalence in a study (which could be a subset in some included studies)

Table S5: Associations between predictors

	Mean age (lm) Unadjusted coefficient estimates	**No of conditions (nb) Unadjusted incident rate ratio**
Mean age		1·0 (1.0-1.0)
Source		
Self-report	59.5 (intercept)	Ref
Database	7.2 (1.7-12.7)*	1.8 (1.5-2.2)***
Continent		
Europe	66.8 (62.7-70.9) (intercept)	Ref
North America	-7.0 (-12.8 to -1.1)*	0.6 (0.5-0.8)***
Australasia	-8.0 (-17.5-1.6)	0.8 (0.6-1.1)
Asia	-8.9 (-15.1 to -2.7)**	0.7 (0.6-0.8)***
South America	-8.5 (-18.1-1.1)	0.6 (0.4-0.9)**
Africa	-32.8 (-57.7 to -8.0)**	0.4 (0.2-0.8)*
Multiple continents	-7.6 (-18.4-3.2)	0.5 (0.3-0.7)***
Setting		
Community	59.8 (intercept)	Ref
Primary care	2.6 (-3.3-8.6)	1.7 (1.4-2.1)***
Hospitals	10.2 (1.5-19.0)*	1.8 (1.3-2.4)***
Study population		
All adults	48.2 (intercept)	Ref
Middle-aged and older	15.5 (12.8-18.1)***	0.9 (0.7-1.1)
Only older people	26.3 (23.8-28.8)***	1.14 (1.0-1.4)

*<0.05 **<0.01 ***<0.001

Ref: Reference category. lm: Linear regression. nb: Negative binomial regression

Table S6: Risk of bias assessment of included studies

Author	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Publication bias	Conflict of interest	Overall rating	Reporting of MM measure and definition
1. Aarts et al (2012)	Moderate	Moderate	Moderate	High	Low	Low	Moderate	Low	Moderate	Yes
2. Aarts et al (2011)	Low	High	Moderate	High	Moderate	Moderate	Moderate	Low	Moderate	No
3. Aarts et al (2011)	Moderate	Moderate	Moderate	High	Low	Low	Moderate	Low	Moderate	Yes
4. Abizanda et al (2014)	Moderate	Moderate	Moderate	High	Moderate	Moderate	Moderate	Low	Moderate	Yes
5. Agborsangaya et al (2012)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
6. Agborsangaya et al (2013)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
7. Agborsangaya et al (2014)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
8. Ahrenfeldt et al (2019)	Low	Moderate	Moderate	High	Low	High	Moderate	Low	Moderate	No
9. Alimohammadian et al (2017)	Low	Moderate	Moderate	High	Low	High	Moderate	Low	Moderate	Yes
10. Angst et al (2002)	Moderate	Moderate	Moderate	High	Low	High	High	Unclear	High	No
11. Appa et al (2014)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
12. Adams et al (2017)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
13. Ahmadi et al (2016)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
14. Amaral et al (2018)	High	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes

Author	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Publication bias	Conflict of interest	Overall rating	Reporting of MM measure and definition
[15.] An et al (2016)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[16.] Araujo et al (2018)	Low	Moderate	Low	High	Moderate	High	Moderate	Low	Moderate	Yes
[17.] Arnold-Reed et al (2018)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[18.] Arokiasamy et al (2015)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[19.] Sinnige et al (2015)	Low	Moderate	Moderate	High	Low	Low	Moderate	Low	Moderate	Yes
[20.] Zemedikun et al (2018)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[21.] Wensing et al (2001)	Moderate	Moderate	Moderate	High	Moderate	Moderate	Moderate	Unclear	Moderate	Yes
[22.] Mounce et al (2018)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[23.] Taylor et al (2010)	Low	Moderate	Moderate	High	Low	Low	Moderate	Low	Low	Yes
[24.] Vancampfort et al (2019)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[25.] Vancampfort et al (2018)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[26.] Aubert et al (2016)	Moderate	Moderate	Moderate	High	Moderate	Low	Moderate	Low	Moderate	Yes
[27.] Autenrieth et al (2013)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[28.] Bahler et al (2015)	Low	Moderate	Moderate	High	Moderate	Low	Moderate	Low	Moderate	Yes
[29.] Vancampfort et al (2017)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes

Author	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Publication bias	Conflict of interest	Overall rating	Reporting of MM measure and definition
[30.] Banjare et al (2014)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[31.] Barra et al (2015)	Moderate	Moderate	High	High	Moderate	High	Moderate	Unclear	Moderate	No
[32.] Bernard et al (2016)	High	Moderate	High	High	Moderate	Low	Moderate	Low	High	No
[33.] Biswas et al (2019)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	No
[34.] Blakemore et al (2016)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	No
[35.] Blyth et al (2008)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[36.] Bowling et al (2019)	Low	Moderate	Moderate	High	Moderate	Low	Moderate	Low	Moderate	Yes
[37.] Britt et al (2008)	Low	Moderate	High	High	Moderate	Moderate	Moderate	Low	Moderate	Yes
[38.] Broeiro-Goncalves (2019)	Low	Moderate	High	High	Moderate	Moderate	Moderate	Low	Moderate	Yes
[39.] Bruce et al (2010)	High	Moderate	Moderate	High	Low	High	Moderate	Unclear	High	No
[40.] Burgers et al (2010)	Low	Moderate	High	High	Moderate	Low	Moderate	Low	Moderate	Yes
[41.] Burke et al (2017)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[42.] Buurman et al (2016)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[43.] Calderon-Larranaga et al (2017)	Moderate	Moderate	Moderate	High	Low	Low	Moderate	Low	Moderate	Yes
[44.] Camargo-Casas et al (2018)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes

Author	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Publication bias	Conflict of interest	Overall rating	Reporting of MM measure and definition
[45.] Canevelli et al (2019)	High	High	High	High	Moderate	High	Moderate	Low	High	Yes
[46.] Chamberlain et al (2020)	Low	Moderate	Moderate	High	Low	Low	Moderate	Low	Low	Yes
[47.] Chen et al (2018)	Low	Moderate	High	High	Low	Low	Moderate	Low	Low	Yes
[48.] Chen et al (2018)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[49.] Cheung et al (2013)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[50.] Chu et al (2018)	Low	Moderate	Moderate	High	Moderate	Moderate	Moderate	Low	Moderate	Yes
[51.] Chudasama et al (2019)	Moderate	Moderate	Low	High	Moderate	Low	Moderate	Low	Moderate	Yes
[52.] Cimarras-Otal et al (2014)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[53.] Chin et al (2016)	Moderate	Moderate	Moderate	High	Moderate	Low	Moderate	Low	Moderate	Yes
[54.] Agrawal et al (2016)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[55.] Gu et al (2018)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[56.] Gunn et al (2012)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[57.] Han et al (2013)	High	High	Moderate	High	Moderate	High	Moderate	Unclear	High	No
[58.] Hanlon et al (2018)	Low	Moderate	Moderate	High	Low	Low	Moderate	Low	Low	Yes
[59.] Jantsch et al (2018)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes

Author	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Publication bias	Conflict of interest	Overall rating	Reporting of MM measure and definition
[60.] John et al (2003)	Moderate	High	Moderate	High	Low	High	Moderate	Low	High	No
[61.] Johnson-Lawrence et al (2017)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[62.] Johnston et al (2019)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	No
[63.] Jones et al (2016)	Low	Moderate	Moderate	High	Low	Low	Moderate	Unclear	Moderate	Yes
[64.] Jovic et al (2016)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[65.] Juul-Larsen et al (2020)	High	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[66.] Hudon et al (2008)	Low	Moderate	Moderate	High	Low	Low	Moderate	Low	Low	Yes
[67.] Hussain et al (2015)	Moderate	Moderate	High	High	Moderate	Low	Moderate	Low	Moderate	Yes
[68.] Ie et al (2017)	High	High	Moderate	High	Moderate	Low	Moderate	Low	High	Yes
[69.] Ishizaki et al (2019)	Moderate	Moderate	Low	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[70.] Danon-Hersch et al (2012)	Moderate	High	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[71.] de Heer et al (2013)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[72.] Demirchyan et al (2013)	High	Moderate	Low	High	Moderate	High	Moderate	Low	High	No
[73.] Fabbri et al (2015)	Moderate	Moderate	High	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[74.] Fillenbaum et al (2000)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes

Author	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Publication bias	Conflict of interest	Overall rating	Reporting of MM measure and definition
[75.] Kaneko et al (2019)	Moderate	Moderate	High	High	Moderate	Low	Moderate	Low	Moderate	No
[76.] Kang et al (2017)	High	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[77.] Gandhi et al (2020)	Moderate	Moderate	Moderate	High	High	High	Moderate	Low	Moderate	Yes
[78.] Costa et al (2018)	High	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[79.] Rizzuto et al (2017)	High	Moderate	High	High	Moderate	Moderate	Moderate	Low	Moderate	Yes
[80.] Dhalwani et al (2017)	Moderate	Moderate	Low	High	Moderate	High	Moderate	Low	Moderate	Yes
[81.] Elixhauser et al (1998)	Low	Moderate	High	High	Low	Low	Moderate	Unclear	Low	Yes
[82.] Fabbri et al (2015)	High	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[83.] Fortin et al (2014)	Low	Moderate	Low	High	Moderate	Moderate	Moderate	Low	Moderate	Yes
[84.] Fuchs et al (1998)	Moderate	Moderate	Moderate	High	Moderate	Low	Moderate	Unclear	Moderate	No
[85.] Galenkamp et al (2011)	Low	Moderate	High	High	Moderate	High	Moderate	Unclear	High	No
[86.] Galenkamp et al (2016)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[87.] Gamma et al (2001)	High	Moderate	High	High	Moderate	High	Moderate	Unclear	High	No
[88.] Ge et al (2018)	Moderate	Moderate	High	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[89.] Ge et al (2019)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes

Author	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Publication bias	Conflict of interest	Overall rating	Reporting of MM measure and definition
[90.] Gould et al (2016)	Moderate	Moderate	Moderate	High	High	High	Moderate	Unclear	Moderate	Yes
[91.] Habib et al (2014)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	No
[92.] Harrison et al (2017)	Low	Moderate	High	High	Moderate	Low	Moderate	Unclear	Moderate	No
[93.] Hayek et al (2017)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[94.] Henninger et al (2012)	Moderate	Moderate	High	High	Moderate	High	Moderate	Unclear	Moderate	No
[95.] Hernandez et al (2019)	Moderate	Moderate	Moderate	High	High	High	Moderate	Unclear	Moderate	Yes
[96.] Ho et al (2014)	Moderate	Moderate	High	High	Low	Low	Moderate	Low	Moderate	Yes
[97.] Khan et al (2019)	Low	Moderate	Low	High	Low	High	Moderate	Low	Low	Yes
[98.] Kiliari et al (2013)	High	Moderate	High	High	Moderate	Moderate	Moderate	Low	Moderate	No
[99.] King et al (2018)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[100.] Kingston et al (2018)	Low	Moderate	High	High	Moderate	High	Moderate	Unclear	High	Yes
[101.] Koyanagi et al (2018)	Low	Moderate	Moderate	High	Moderate	Low	High	Low	Moderate	Yes
[102.] Kriegsman et al (2004)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[103.] Kristensen et al (2019)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[104.] Kristensen et al (2019)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes

Author	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Publication bias	Conflict of interest	Overall rating	Reporting of MM measure and definition
[105.] Kunna et al (2017)	Low	Moderate	Low	High	Moderate	Low	High	Low	Low	Yes
[106.] Kuwornu et al (2014)	Moderate	Moderate	High	High	Moderate	Low	Moderate	Low	Moderate	Yes
[107.] Lai et al (2019)	Low	Moderate	High	High	Moderate	Low	Moderate	Low	Moderate	Yes
[108.] Lai et al (2018)	High	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[109.] Laires et al (2019)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[110.] Lang et al (2015)	Moderate	Moderate	Moderate	High	Moderate	Moderate	Moderate	Low	Moderate	Yes
[111.] Le Cossec et al (2016)	Low	Moderate	Moderate	High	Moderate	Moderate	Moderate	Low	Moderate	Yes
[112.] Lee et al (2007)	Low	Moderate	High	High	Low	Low	Moderate	Low	Low	Yes
[113.] Lee et al (2018)	Low	Moderate	High	High	High	Low	Moderate	Unclear	High	No
[114.] Li et al (2016)	Low	Low	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[115.] Li et al (2019)	Low	Moderate	Low	High	Moderate	Moderate	Moderate	Low	Moderate	No
[116.] Lujic et al (2017)	Low	Moderate	Moderate	High	Low	High	Moderate	Low	Moderate	Yes
[117.] LupianezUnclearVillanueva et al (2018)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[118.] Zhou et al (2018)	Moderate	Moderate	Moderate	High	Moderate	Low	High	Low	Moderate	Yes
[119.] Zhang et al (2019)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes

Author	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Publication bias	Conflict of interest	Overall rating	Reporting of MM measure and definition
[120.] Wong et al (2010)	High	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[121.] Weimann et al (2016)	Low	Moderate	Low	High	Moderate	High	Moderate	Low	Moderate	Yes
[122.] Wang et al (2017)	Low	Moderate	Low	High	Moderate	High	Moderate	Low	Moderate	Yes
[123.] Wang et al (2019)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	No
[124.] Wade et al (2019)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[125.] Maciejewski et al (2019)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[126.] Marengoni et al (2016)	Moderate	Moderate	High	High	Moderate	High	Moderate	Low	Moderate	Yes
[127.] Marengoni et al (2009)	Moderate	Moderate	High	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[128.] Marques et al (2018)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[129.] Mavaddat et al (2014)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[130.] McDaid et al (2013)	Low	Moderate	High	High	Moderate	High	Moderate	Low	High	Yes
[131.] Melis et al (2014)	High	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[132.] Min et al (2007)	High	Moderate	High	High	Moderate	High	Moderate	Unclear	High	Yes
[133.] Momtaz et al (2010)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[134.] Mondor et al (2018)	Low	Moderate	Low	High	Moderate	High	Moderate	Low	Moderate	Yes

Author	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Publication bias	Conflict of interest	Overall rating	Reporting of MM measure and definition
[135.] Muggah et al (2012)	Low	Moderate	High	High	Moderate	Low	Moderate	Low	Moderate	No
[136.] Nagel et al (2008)	Low	Moderate	Low	High	Moderate	High	Moderate	Low	Moderate	Yes
[137.] Niedzwiedz et al (2019)	Moderate	Moderate	High	High	Moderate	Low	Moderate	Unclear	Moderate	Yes
[138.] Nunes et al (2016)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[139.] Nunes et al (2017)	Low	Moderate	Moderate	High	Low	High	Moderate	Low	Moderate	Yes
[140.] Nunes et al (2015)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[141.] Olaya et al (2017)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[142.] Olivares et al (2017)	High	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	No
[143.] Park et al (2018)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	No
[144.] Patel et al (2006)	Moderate	Moderate	High	High	Moderate	High	Moderate	Unclear	Moderate	No
[145.] Pati et al (2016)	High	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[146.] Pati et al (2019)	Moderate	Moderate	Moderate	High	Moderate	Moderate	Moderate	Low	Moderate	Yes
[147.] Pati et al (2017)	Moderate	Moderate	Moderate	High	Moderate	Moderate	Moderate	Unclear	Moderate	Yes
[148.] Payne et al (2013)	Low	Moderate	Moderate	High	Moderate	Low	Moderate	Unclear	Moderate	Yes
[149.] Perez et al (2020)	Moderate	Moderate	Moderate	High	Moderate	Moderate	Moderate	Low	Moderate	Yes

Author	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Publication bias	Conflict of interest	Overall rating	Reporting of MM measure and definition
[150.] Petersen et al (2019)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	No
[151.] Pfortmueller et al (2013)	Moderate	Moderate	High	High	High	High	Moderate	Unclear	High	No
[152.] Pressley et al (1999)	Low	Moderate	High	High	Moderate	Low	Moderate	Unclear	Moderate	No
[153.] Prior et al (2016)	Low	Moderate	Moderate	High	Moderate	Low	Moderate	Unclear	Moderate	Yes
[154.] Ribeiro et al (2018)	High	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[155.] Ruel et al (2014)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[156.] Ruel et al (2014)	Moderate	Moderate	Moderate	High	Low	High	Moderate	Low	Moderate	Yes
[157.] Ryan et al (2018)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[158.] Schmidt et al (2016)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[159.] Schottker et al (2016)	Moderate	Moderate	Moderate	High	Moderate	Moderate	Moderate	Low	Moderate	Yes
[160.] Seo et al (2017)	Low	Moderate	Moderate	High	Low	High	Moderate	Low	Moderate	No
[161.] She et al (2019)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[162.] Singh et al (2019)	Low	Moderate	Moderate	High	Low	Low	Moderate	Unclear	Moderate	Yes
[163.] Stepanova et al (2015)	Low	High	High	High	High	High	High	Unclear	High	Yes
[164.] Stickley et al (2020)	Low	Moderate	High	High	Moderate	High	Moderate	Low	High	Yes

Author	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Publication bias	Conflict of interest	Overall rating	Reporting of MM measure and definition
[165.] Streit et al (2014)	Moderate	Moderate	Moderate	High	High	High	Moderate	Unclear	Moderate	Yes
[166.] Stubbs et al (2018)	Low	Moderate	High	High	Moderate	Low	Moderate	Low	Moderate	Yes
[167.] Su et al (2016)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[168.] Sundstrup et al (2017)	Low	Moderate	High	High	Moderate	High	Moderate	Unclear	High	Yes
[169.] Takahashi et al (2016)	Moderate	Moderate	High	High	High	Low	Moderate	Low	High	No
[170.] Tinetti et al (2011)	Low	Moderate	High	High	High	High	Moderate	Unclear	High	No
[171.] Troelstra et al (2020)	High	Moderate	High	High	Moderate	Low	Moderate	Unclear	High	Yes
[172.] van Zon et al (2020)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[173.] Vancampfort et al (2017)	Low	Moderate	Moderate	High	Moderate	Low	Moderate	Low	Moderate	Yes
[174.] Vassilaki et al (2015)	Low	Moderate	Moderate	High	Moderate	Low	Moderate	Unclear	Moderate	Yes
[175.] Vassilaki et al (2016)	Low	Moderate	Moderate	High	Moderate	Low	Moderate	Unclear	Moderate	Yes
[176.] Villarreal et al (2015)	High	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	No
[177.] Violan et al (2019)	Low	Moderate	Moderate	High	High	Low	Moderate	Low	Moderate	Yes
[178.] von Strauss et al (2000)	Moderate	Moderate	Moderate	High	Moderate	Low	Moderate	Low	Moderate	No
[179.] Vos et al (2013)	Moderate	Moderate	High	High	Moderate	High	Moderate	Low	Moderate	No

Author	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Publication bias	Conflict of interest	Overall rating	Reporting of MM measure and definition
[180.] Vu et al (2019)	High	Moderate	High	High	Moderate	High	Moderate	Low	High	No
[181.] Wang et al (2018)	Moderate	Moderate	Low	High	Moderate	Low	Moderate	Unclear	Moderate	Yes
[182.] Wang et al (2017)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[183.] Wijers et al (2019)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	No
[184.] Williams et al (2016)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	No
[185.] Woldesemayat et al (2018)	High	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[186.] Yao et al (2020)	Moderate	Moderate	Low	High	Moderate	High	Moderate	Low	Moderate	Yes
[187.] Yorke et al (2017)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[188.] You et al (2019)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[189.] Zhang et al (2020)	Moderate	Moderate	Low	High	Moderate	Low	Moderate	Low	Moderate	Yes
[190.] Khanam et al (2011)	Moderate	Moderate	Moderate	High	Moderate	Low	Moderate	Unclear	Moderate	Yes
[191.] Cornell et al (2009)	Low	Moderate	High	High	Moderate	Low	Moderate	Unclear	Moderate	Yes
[192.] Cassell et al (2018)	Low	Moderate	High	High	Moderate	Moderate	Moderate	Low	Moderate	No
[193.] Wong et al (2019)	High	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[194.] Puth et al (2017)	Moderate	Moderate	Moderate	High	Moderate	Moderate	Moderate	Low	Moderate	Yes

Table S7: Output of adjusted meta-analytic model based on 218 studies

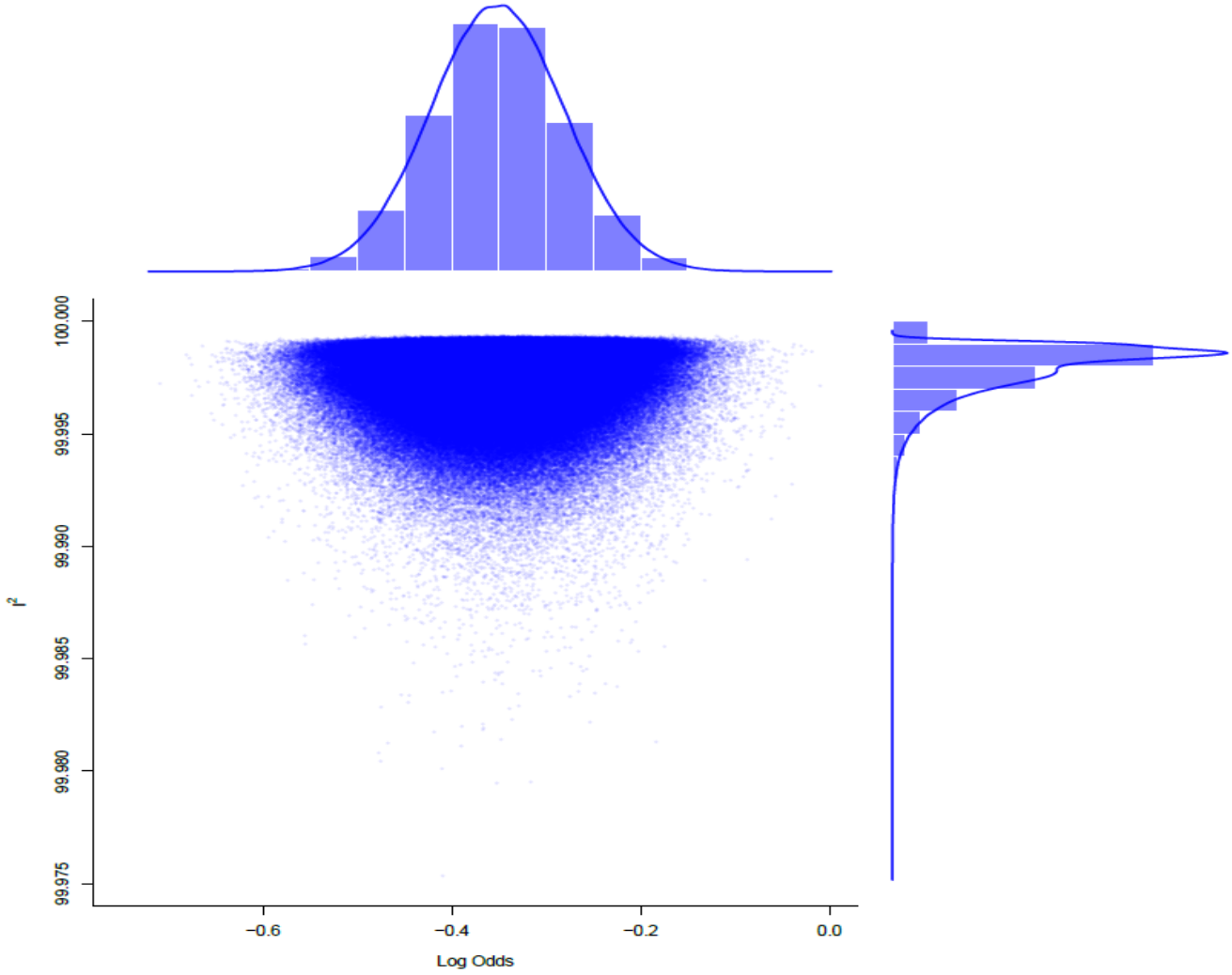
	Pooled prevalence of multimorbidity of each subgroup (%, 95% CI)	Meta-regression Unadjusted Odds Ratio (95% CI)	Meta-regression Adjusted Odds Ratio (95% CI) R^2 45.1%	FMI
Group of mean age		R^2 30.9%		
<59	29.3 (26.2-32.7)	Ref	Ref	Ref
59-73	47.0 (41.3-52.7)	2.1 (1.6-2.8)***	2.5 (2.0-3.2)***	0.3
≥74	66.1 (60.5-71.2)	4.7 (3.4-6.4)***	4.4 (3.3-5.9)***	0.2
No of conditions		R^2 6.2%		
<9	30.8 (26.0-35.9)	Ref	Ref	Ref
9-19	45.0 (40.8-49.3)	1.8 (1.3-2.6)***	1.8 (1.4-2.3)***	0.1
20-43	44.3 (35.7-53.3)	1.8 (1.2-2.7)**	1.8 (1.2-2.5)**	0.2
≥44	51.6 (32.3-70.4)	2.4 (1.3-4.3)**	2.5 (1.5-4.0)***	0.2
Setting		R^2 3.3%		
Community	38.2 (34.9-41.7)	Ref	Ref	Ref
Primary care	50.6 (41.2-59.9)	1.7 (1.2-2.4)**	1.8 (1.3-2.6)***	0.2
Hospital	47.1 (31.9-63.0)	1.4 (0.9-2.4)	1.0 (0.7-1.6)	0.09
Care home	73.9 (72.8-74.9)	4.6 (0.6-34.5)	1.8 (0.3-9.2)	0.03
Source		R^2 2.7%		
Self-report	38.6 (34.8-42.4)	Ref	Ref	Ref
Database	48.9 (42.3-55.5)	1.5 (1.1-2.1)**	0.8 (0.6-1.1)	0.1
Continent		R^2 5.3%		
North America	48.9 (42.0-55.7)	Ref	Ref	Ref
Europe	44.0 (37.7-50.4)	0.8 (0.6-1.2)	0.6 (0.4-0.8)***	0.1
Australasia	28.2 (20.3-37.6)	0.4 (0.2-0.7)**	0.4 (0.3-0.7)***	0.07
Asia	34.2 (28.6-40.3)	0.5 (0.4-0.8)**	0.5 (0.4-0.7)***	0.1
South America	47.5 (31.2-64.4)	0.9 (0.5-1.8)	0.8 (0.5-1.4)	0.1
Africa	23.6 (12.3-32.8)	0.3 (0.1-0.9)*	0.3 (0.2-0.8)*	0.1
Multiple continents	41.4 (31.0-52.6)	0.7 (0.4-1.4)	0.6 (0.4-1.1)	0.1

*<0.05 **<0.01 ***<0.001
Ref: Reference category. FMI: Fraction of missing information.

Table S8: Definition of variables

Variable name	Definition
Study setting	
Community	Studies that used population surveys, insurance claims databases, or research databases
Primary care	Studies that were carried out in primary care settings
Hospital	Studies that were carried out in hospital settings
Data source	
Self-report	Studies that collected data using self-report or interviews
Medical records and administrative databases	Studies that collected data using electronic medical records, medical chart reviews, insurance claims databases, pharmacy databases, or research databases
Study population	
All adults	Studies with a sample of population aged 18 and older (n=45), aged 20 and older (n=8), aged 21 and older (n=3), aged 25 and older (n=2), or others (n=27) (e.g. aged 16 and older, or aged 17 and older)
Middle-aged and older	Studies with a sample of population aged 50 and older (n=25), aged 40 and older (n=5), aged 40 and older (n=10), or others (n=6) (e.g. aged 57 and older, or aged 45 and older)
Only older people	Studies with a sample of population aged 65 and older (n=22), aged 60 and older (n=25), aged 70 and older (n=5) or others (n=11) (e.g. aged 68 and older, aged 77 and older, aged 78 and older, or aged 80 and older)

Figure S1: Graphical display of study effect sizes and heterogeneity



No obvious subgroup effects were identified

Figure S2: Process of examining and identifying outlying studies in meta-analysis

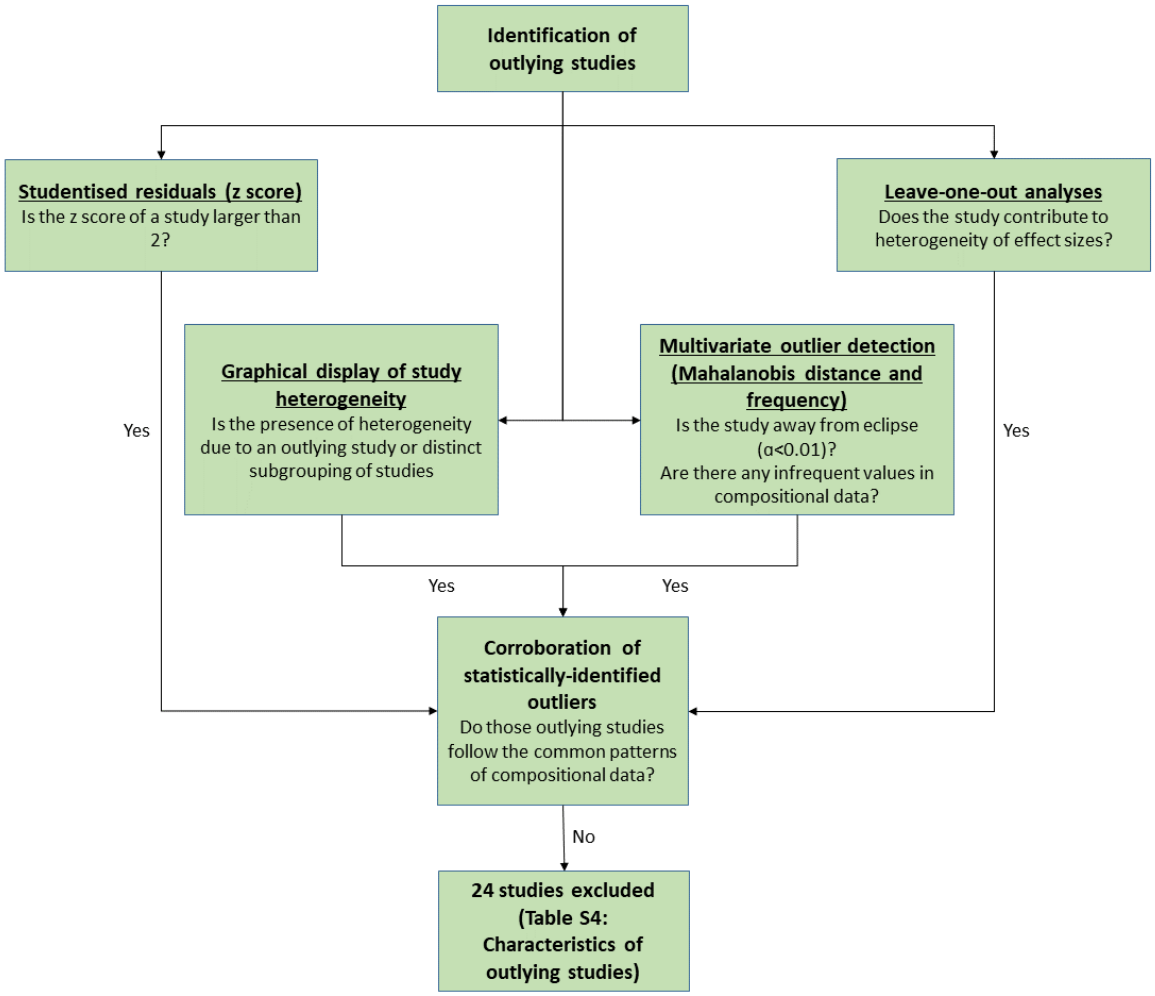


Figure S3: Summary of risk of bias assessment

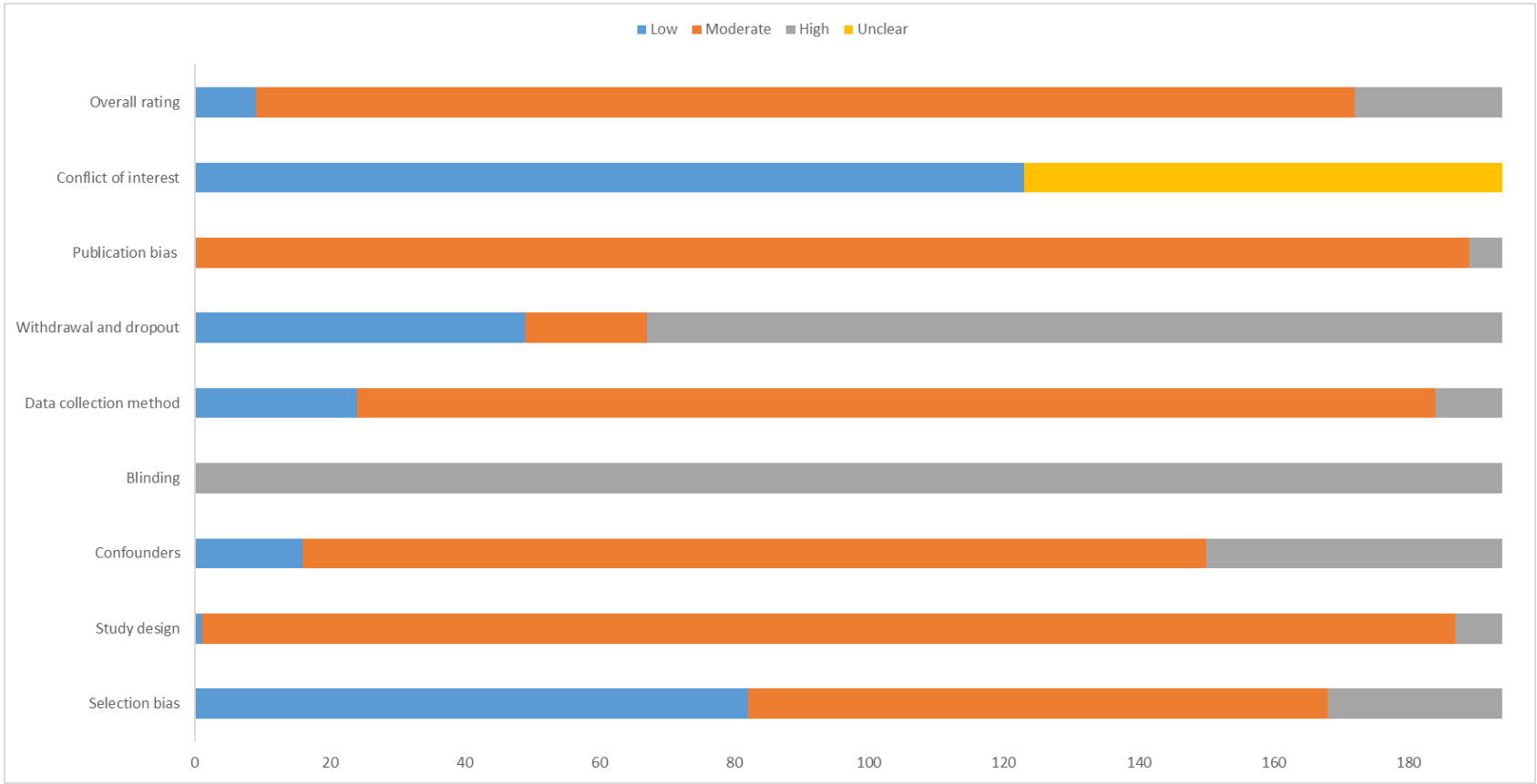
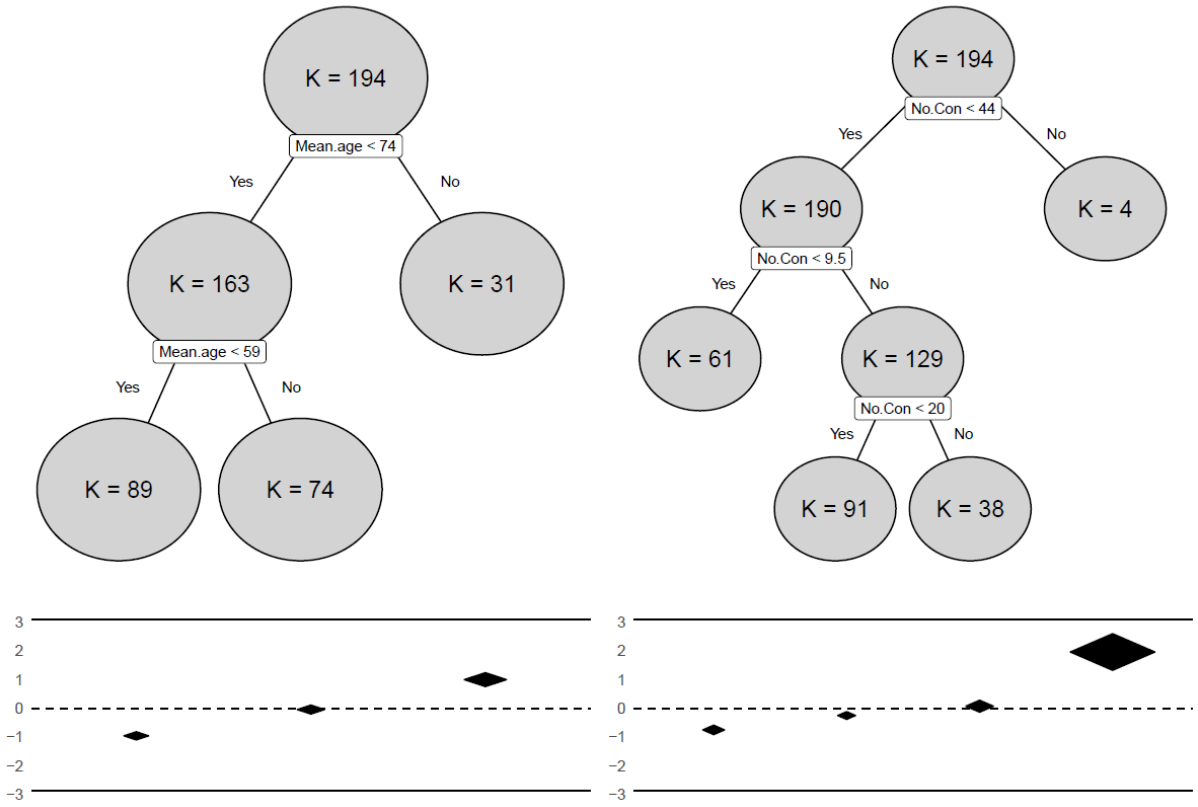


Figure S4: Meta-regression trees for predicting the pooled estimated prevalence of multimorbidity (based on 'mean age' and 'number of conditions' predictors. unit: log(odds))



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PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Table S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 6, Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Supplementary Table S8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 6 Appendix p26
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 6-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 6-8

| Section/topic | # | Checklist item | Reported on page # |

PRISMA Checklist

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 10 and Table 2
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 6-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 8-9, Table 1; Supplementary Table S4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary Table S6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 9-10 Figure 2-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 9-10 Table 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 9-10, Table 1 and Table 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 10-11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 11,12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 14

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Variation in the estimated prevalence of multimorbidity: systematic review and meta-analysis of 193 international studies

Iris Szu-Szu Ho,[1] Amaya Azcoaga-Lorenzo,[2] Ashley Akbari,[3] Professor Jim Davies,[4] Peter Hodgins,[1] Kamlesh Khunti,[5] Umesh Kadam,[5] Ronan A Lyons,[3] Colin McCowan,[2] Stewart W Mercer,[1] Krishnarajah Nirantharakumar,[6] Bruce Guthrie.[1]

1. University of Edinburgh, Usher Institute, Medical School, Teviot Place, Edinburgh, EH8 9AG, United Kingdom
2. University of St Andrews, School of Medicine, Medical and Biological Sciences, North Haugh, St Andrews, KY16 9TF, United Kingdom
3. Swansea University, Medical School, Population Health Science, Singleton Park, Swansea, SA2 8PP, United Kingdom
4. University of Oxford, Department of Computer Science, Wolfson Building, Parks Road, Oxford, OX1 3QD, United Kingdom
5. University of Leicester, Leicester General Hospital, Gwendolen Road, Leicester, LE5 4PW, United Kingdom
6. University of Birmingham, Institute of Applied Health Research, Birmingham, B15 2TT, United Kingdom

Corresponding author: Iris Szu-Szu Ho. Email: iris.s.ho@outlook.com

Abstract

Objective. (1) To estimate the pooled prevalence of multimorbidity in all age groups, globally. (2) To examine how measurement of multimorbidity impacted the estimated prevalence.

Methods. In this systematic review and meta-analysis, we conducted searches in nine bibliographic databases (PsycINFO, Embase, Global Health, Medline, Scopus, Web of Science, Cochrane Library, CINAHL, and ProQuest Dissertations & Theses Global) for prevalence studies published between database inception and 21 January 2020. Studies reporting the prevalence of multimorbidity (in all age groups and in community, primary care, care home and hospital settings) were included. Studies with an index condition or those that did not include people with no long-term conditions in the denominator were excluded. Retrieved studies were independently reviewed by two reviewers, and relevant data were extracted using pre-designed pro-forma. We used meta-analysis to pool the estimated prevalence of multimorbidity across studies, and used random-effects meta-regression and subgroup analysis to examine the association of heterogeneous prevalence estimates with study and measure characteristics.

Results. 13,807 titles were screened, of which 193 met inclusion criteria for meta-analysis. The pooled prevalence of multimorbidity was 42.4% (95%CI=38.9%-46.0%) with high heterogeneity (I^2>99%). In adjusted meta-regression models, participant mean age and the number of conditions included in a measure accounted for 47.8% of heterogeneity in effect sizes. The estimated prevalence of multimorbidity was significantly higher in studies with older adults and those that included larger numbers of conditions. There was no significant difference in estimated prevalence between low- or middle-income countries (36.8%) and high-income countries (44.3%), or between self-report (40.0%) and administrative/clinical databases (52.7%).

Conclusions. The pooled prevalence of multimorbidity was significantly higher in older populations and when studies included a larger number of baseline conditions. The findings suggest that, to improve study comparability and quality of reporting, future studies should use a common core conditions set for multimorbidity measurement and report multimorbidity prevalence stratified by socio-demographics.

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Strengths and limitations of this study

- This study used meta-regression to examine the variation of estimated prevalence of multimorbidity and how measure and study characteristics influenced prevalence estimates.
- The use of multiple imputation in this study minimised biased estimates caused by missing values and unbalanced classes and enhanced statistical accuracy.
- The inclusion of studies with various measure and study characteristics enabled a better understanding of the contributing factors of the heterogeneity of multimorbidity prevalence.
- Due to inconsistent reporting of multimorbidity prevalence and data unavailability, the estimated multimorbidity prevalence stratified by sex, ethnicity and socio-economic status could not be explored in this study.

Introduction

Population ageing is a worldwide phenomenon, with the World Health Organization (WHO, 2018) estimating that the proportion of the global population aged 60 and older will double from 12% to 22% between 2015 and 2050 [1]. A key implication of population ageing is that increasing numbers of people will be living with multimorbidity. Multimorbidity, commonly defined as the co-occurrence of two or more long-term conditions [2], adversely affects people's risk of death, health-related quality of life, functional ability, and mental well-being [3, 4]. Multimorbdiity affects all groups of society, but is known to be more common in older people, in women, and in those from low socio-economic backgrounds particularly in high-income countries [5-7]. In low- and middle-income countries, people living in urban areas, on the other hand, were found to have a higher rate of multimorbidity prevalence [8]. Multimorbidity poses major challenges to the delivery of care in health systems internationally which are often focused on the management of single diseases and lack appropriate coordination and continuity of care across different sectors [9, 10]. Disparities in health and health and social care could be found at any stage along the continuum of chronic diseases, from prevention to the management of diseases. To understand these disparities among multimorbid populations requires consistently monitoring the populations (e.g. incidence, prevalence, health impact, risk factors and delivery of care) defined by race and ethnicity, gender, age, socio-economic status, physical environment and geographic factors.

Previous systematic reviews have identified issues in the measurement of multimorbidity, related to the choice of chronic conditions counted in measures, the categorisation of conditions and diseases, and the counting or weighting method used [11-13]. Although weighted measures are often used when the purpose of measurement is to predict future outcomes, a simple count of conditions remains the most commonly-used method for the measurement of multimorbidity, and is optimal for estimating multimorbidity prevalence [13, 14]. However, the estimated prevalence of multimorbidity varies widely in the literature ranging from 3.5% to 100% [15], likely reflecting a combination of varying measures and varying populations studied [16]. Much of the research up to now has not quantitatively investigated the variation in multimorbidity prevalence and its influencing factors in much detail. Understanding the links between prevalence estimates and measurement approaches can better inform and support future development of multimorbidity measurement guidelines. Therefore, this review aimed to examine the pooled prevalence of

multimorbidity in all age groups, globally and how measurement of multimorbidity impacted the estimated prevalence.

Research questions

- What is the pooled prevalence of multimorbidity and does it differ between different age groups?
- What are the factors that influenced the variation in prevalence estimates across studies?

Methods

The systematic review and meta-analysis reported here is part of a larger review which aimed to examine 1) how multimorbidity has been constructed and 2) measured by international studies and 3) variation in the estimated prevalence of multimorbidity across studies. Analysis in relation to the first two registered objectives has been reported [13], and this paper reports the third registered objective. The PROSPERO registration number for this paper is therefore the same as for the first published paper from this work [13].

Inclusion and exclusion criteria

The eligibility criteria for this review were defined based on the CoCoPop framework—Condition, Context, and Population [17]. The condition included in this review is prevalence of multimorbidity. The majority of studies defined multimorbidity as the co-existence of two or more chronic conditions, and used the cut-off to estimate its prevalence in a population of interest. We therefore included studies that used this definition for examining multimorbidity prevalence across international studies. For this analysis, we included studies carried out in the community, primary care, care home and hospitals, and those estimating the prevalence of multimorbidity in the population studied. Studies that did not include a relevant denominator population – for example, only examining patients with an index condition or excluding patients who did not have multimorbidity – were excluded. Qualitative research, studies not published in English, and conference abstracts were also excluded.

Search strategy

The search strategy for this review was developed in collaboration with a specialist medical librarian (Supplementary Table S1). Key terms relevant to multimorbidity and measurement were

combined using Boolean logic to identify studies that met the inclusion criteria. We included medical subject headings to provide a sensitive search for relevant literature. Databases included in the search were Ovid interface (PsycINFO, Embase, Global Health, Medline), Scopus, Web of Science, Cochrane Library, EBSCO interface (CINAHL Plus), and ProQuest Dissertations & Theses Global, from inception to 21 January 2020 (we are not aware of any large recently published studies since that date). In addition to the database searches, our secondary search strategy included hand-searching reference lists of retrieved articles and tracked citations to maximise the yield.

Study screening and selection

Articles retrieved from databases were organised using EndNote X9 bibliographic software and Excel, and then were imported to Covidence for screening [18]. Titles, abstracts, and full-texts of retrieved articles were screened against the eligibility criteria by two reviewers. Throughout the review process, any disagreement that arose was resolved through discussion between the two reviewers (IS-SH and PH), and through the involvement of a third reviewer (BG) if necessary. The study selection process is summarised in Figure 1.

Data extraction

We extracted data on the characteristics of the included studies using pre-designed data extraction pro-forma. The extracted data include 1) authors, 2) publication year, 3) study purpose, 4) method, 5) country, 6), continent, 7) country income (classified as 'high' and 'low or medium' [combined because of small numbers] allocated based on the World Bank Group at the time of review [19]), 8) study participants, 9) mean age, 10) sample size, 11) number of conditions, 12) setting, 13) data collection method/data source, 14) number of multimorbidity cases, and 15) proportion of multimorbidity (calculated based on item 10 and 14). Data on the estimated prevalence stratified by sex, ethnicity and socio-economic status were fragmented and unavailable in many studies, and thus these could not be retrieved for analyses.

Risk of bias assessment

We used the Effective Public Health Practice Project (EPHPP) quality assessment tool for quantitative studies to assess the risk of bias and the quality of each of the included studies, in terms of 1) selection bias, 2) study design, 3) confounders, 4) blinding, 5) data collection method, 6) withdrawals and dropouts [20]. We assessed also publication bias (rated high if there was

selective reporting within studies) and conflict of interest (rated unclear if conflict of interest declaration was not reported). Each study was rated and assigned an overall risk of bias as 'high', 'moderate', or 'low' (please see the details in appendix p26).

Data analysis

Descriptive statistics were used to summarise study characteristics. Since distributions were skewed, median and interquartile range were used to measure the central tendency and examine variability of variables such as mean age and number of conditions. Categorical (e.g. continent, study population, and data source) and ordinal data (e.g. country income and risk of bias) were examined using frequency tables. To investigate the association between continuous/count predictor (mean age/number of conditions) and categorical predictors, univariate generalized linear models were used. We summarised the prevalence of multimorbidity using metaprop [21, 22]. The presence of effect size heterogeneity was examined using the Q statistic and I-squared. Significant heterogeneity was identified, so we used subgroup analysis and meta-regression with random-effects models to identify potential moderating factors.

Outlying studies were identified using studentised residuals, leave-one-out analysis and Mahalanobis distance. Studies with studentised residuals that were larger than 2 or 3 and those that contributed to heterogeneity in leave-one-out analyses were scrutinized [23]. Mahalanobis distance was used for pattern recognition and multivariate outlier detection [24]. Study effect sizes were graphically displayed to identify outlying studies and explore subgroup effects (Supplementary Figure S1). In initial analysis of heterogeneity and outliers, 24 studies were found to make a significant contribution to the high level of observed heterogeneity in multimorbidity prevalence and significant changes in the summary effect size. The 24 studies were excluded for one or more of the following reasons: 1) their contribution to high levels of heterogeneity in the leave-one-out test, 2) being identified as an outlying value in the studentised residuals test (z-score ≥ 2), 3) their Mahalanobis distance exceeding the chi-squared critical value at a 0.01 significance level, 4) infrequent values in compositional categorical data (e.g. only one study examined prevalence in children). The process of identifying outliers, the rationale for exclusion of each study, and the characteristics of outlying studies are documented in Supplementary Figure S2 and Table S2 and Table S3. Sensitivity analysis was performed to explore the impact of excluding the 24 studies in meta-analysis.

There was missingness in two predictors, with 37% missingness in the 'mean age' of the study population variable (some of which reported it categorically, and thus were treated as missing data) and 6% missingness in the 'number of conditions' included in the multimorbidity measure variable. Previous research has shown that complete case removal (removing missing data in a data set) in meta-regression could lead to biased coefficient estimates of predictors (varied widely from complete-data estimates), whereas multiple imputation was found to perform well at generating estimates that were close to complete-data estimates [25]. Therefore, in this review, multiple imputation with 60 imputed datasets and 10 iterations was conducted where random forest was used to impute missing data [26, 27]. Following multiple imputation, fraction of missing information (FMI) was computed to quantify the impact of missing data, which ranged from 0.05 to 0.3 indicating that the uncertainty in the values imputed for missing data is small/moderate [28].

A random-effects regression tree approach with ten-fold cross-validation was used to identify subgroups (cut-offs) of the 'mean age' and 'number of conditions' variables with differential effect sizes [29]. Given considerable variation in the effect sizes, we conducted meta-regression with the restricted maximum likelihood (REML) estimator to examine the possible sources of heterogeneity in effect sizes [21, 22, 30]. As the variable 'multimorbidity prevalence' did not follow the normal distribution (positively skewed), we applied logit transformation to the variable for analyses and converted the logits back to odds ratios (e^{logit}) and proportions ($p=e^{logit}/e^{logit}+1$) for reporting. For model selection, we refitted the models using maximum likelihood and then conducted a log-likelihood test to compare the fit of models [31]. A permutation test with 1000 permuted datasets was conducted to validate the robustness of the final model by rearranging and shuffling the order of the data and re-calculating p-values to check whether there is type 1 error [32]. Subgroup analysis with the REML method was used to estimate the pooled multimorbidity prevalence of subgroups of each variable (age, the number of conditions included in a measure, setting, data source, continent, country income, study risk of bias). Forest-like plots were used to display the effect sizes of included studies [33]. The presence of publication bias was assessed using Egger's test, which did not find evidence of publication bias [34]. All statistical tests were performed using R version 4.0.4.

Patients and public involvement

No patients were involved in the development of the research question, outcome measures, study design and implementation. Nonetheless, we have previously discussed preliminary review findings and issues relevant to multimorbidity measurement with our patient and public involvement group. We plan to disseminate the review findings to researchers, clinicians, policy makers and public audiences through news media, social media and seminars.

Results

After screening 13,807 titles and abstracts, 217 studies were identified which estimated the prevalence of multimorbidity using a cut-off of 'two or more' conditions. Following the removal of 24 outlying studies, 193 studies were included in the meta-analysis (Table 1, Supplementary Table S4). Of the 193 studies, 64 studies were from Europe, 47 from North America, 44 from Asia, 11 from Australasia, 12 from South America, and four from Africa (Table 1 and Figure 2).

Seventy-five percent of studies were from high-income countries (n=145) and 24.9% from low- and middle-income countries (LMICs) (one from low-income, eight from lower middle-income, 29 from upper middle-income, and 10 from multiple low- and middle-income countries). The majority of studies (n=147) estimated the prevalence of multimorbidity in community settings, followed by primary care (n=32) and hospital setting (n=14). Prevalence data were collected through either self-report (n=150) or medical records and administrative databases (n=43). In a univariate linear regression (Supplementary Table S5), we found that studies from Europe, database studies and studies conducted in hospital settings were more likely to measure multimorbidity in an older population and included a larger number of conditions in a multimorbidity measure, compared to those from other continents, self-report studies, and studies conducted in primary care and community settings. In respect to risk of bias in included studies (Supplementary Table S6 and Figure S3), 11.4% were rated as high risk of bias, 83.9% as moderate risk of bias, and 4.7% as low risk of bias.

The pooled estimate of multimorbidity prevalence across the 193 studies was 42.4% (95%CI 38.9%-46.0%), τ^2 is 1.0 (95%CI 0.9-1.3) with high heterogeneity (I^2>99%), and meta-regression was therefore used to examine study characteristics associated with heterogeneity. Mean age ($F=89.8$, $p<0.0001$, $R^2=31.7\%$) and number of conditions ($F=39.2$, $p<0.0001$, $R^2=16.7\%$) were the strongest univariate predictors and positively associated with the estimated prevalence of

multimorbidity (Figure 3). Meta-regression tree analysis (Supplementary Figure S4) partitioned the mean age variable into three homogeneous subgroups (aged <59, aged 59-73, aged ≥74) and the number of conditions variable into four homogeneous subgroups (<9, 9-19, 20-43, ≥44). The categorical 'mean age' and 'number of conditions' variables explained 35.9% and 19.5% of the heterogeneity in effect sizes respectively (larger than the original numerical variables). Therefore, the categorical variables identified from the regression trees for meta-analyses were used for meta-regression.

In univariate meta-regression, primary care studies (pooled multimorbidity prevalence 50.5%, OR 1.6, 95%CI 1.1-2.3) and hospital based studies (pooled multimorbidity prevalence 59.6%, OR 2.3, 95%CI 1.3-4.0) had significantly higher rates of multimorbidity than community-based studies (39.1%) (Table 2). Multimorbidity prevalence was significantly higher in database studies (pooled multimorbidity prevalence 52.7%, OR 1.7, 95%CI 1.2-2.4) than self-report studies (pooled multimorbidity prevalence 40.0%). In the mean age categorical variable, the pooled prevalence estimates of the three subgroups were statistically significantly different from one another, and considerably higher in studies with mean participant age ≥74 (pooled multimorbidity prevalence 67.0%, OR 5.2, 95%CI 3.8-7.2) and mean participant age 59-73 (pooled multimorbidity prevalence 47.6%, OR 2.3, 95%CI 1.8-3.0) than those with mean participant age <59 (pooled multimorbidity prevalence 28.0%) (Table 2 and Figure 4). Similar patterns were also found in the number of conditions variable where studies including ≥44 conditions in measurement (pooled multimorbidity prevalence 87.6%, OR 16.5, 95%CI 6.4-42.6), 20-43 conditions (pooled multimorbidity prevalence 52.1%, OR 2.5, 95%CI 1.7-3.7), and 9-19 conditions (pooled multimorbidity prevalence 43.7%, OR 1.8, 95%CI 1.3-2.5) yielded higher prevalence estimates than studies including <9 conditions in measurement (pooled multimorbidity prevalence 30.1%) with a dose-response relationship. The estimated prevalence of multimorbidity was 44.3% in high-income countries compared to 36.8% in low or middle income countries, but the difference was not statistically significantly different (OR 1.4, 95%CI 1.0-1.9). In study risk of bias, no statistically significant difference in pooled prevalence of multimorbidity was found between studies with low, moderate and high risk of bias.

In the adjusted meta-regression model, compared to studies where participant mean age was <59, multimorbidity prevalence remained significantly higher in studies with mean participant age 59-73 (OR 2.2, 95%CI 1.7-2.8) and in studies with mean participant age ≥74 (OR 4.4, 95%CI 3.3-

5.9). Compared to measures including <9 conditions, multimorbidity prevalence was higher in measures including ≥44 conditions (OR 8.2, 95%CI 3.8-17.5), 20-43 conditions (OR 2.3, 95%CI 1.6-3.2), and 9-19 conditions (OR 1.8, 95%CI 1.4-2.3). In respect to study settings, the pooled prevalence was significantly higher in primary care settings compared to community settings (OR 1.6, 95%CI 1.1-2.3). Compared to studies from North America, prevalence was lower in studies from Europe (OR 0.5, 95%CI 0.4-0.7), Australasia (OR 0.5, 95%CI 0.3-0.8), Asia (OR 0.6, 95%CI 0.4-0.8), or Africa (OR 0.3 95%CI 0.1-0.6). No significant difference in prevalence estimates between self-report and routine database studies was evident after controlling for study and measure characteristics. The model explained 54.3% of the heterogeneity in multimorbidity prevalence, with the mean age and number of conditions variables providing most explanatory power (47.8% of the heterogeneity).

Sensitivity analysis including the 24 outlying studies (Supplementary Table S7) was similar to primary analysis except for "number of conditions" variable. The mean participant age and number of conditions variables remained the strongest predictors of multimorbidity prevalence in sensitivity analysis. However, the estimated prevalence in sensitivity analysis (including outlying studies) was much lower in studies including ≥44 conditions in a multimorbidity measure (pooled multimorbidity prevalence 54.5, OR 2.8, 95%CI 1.5-5.4) compared to primary analysis excluding outlying studies (pooled multimorbidity prevalence 87.6, OR 16.5, 95%CI 6.4-42.6). The difference in estimates was mainly attributed to the three outlying studies that included 146, 147 and 259 conditions in a measure respectively but yielded relatively low mean multimorbidity prevalence (mean prevalence 54.3%)[35-37].

Discussion

The overall estimate of multimorbidity prevalence in adults across all the included studies was 42.4% (95%CI=38.9%-46.0%), but with very high heterogeneity. More than half of the observed heterogeneity was explained by study mean participant age and the number of conditions included in the multimorbidity measure, with older age and larger number of conditions strongly associated with a higher prevalence of multimorbidity. The difference in estimated prevalence was small between self-report and administrative/clinical databases, and between study settings. No significant difference was found between studies from low- or middle-income and high-income

countries, but North American studies had higher estimated prevalence and African studies had the lowest estimated prevalence than other continents.

Three prior systematic reviews examined the prevalence of multimorbidity across studies [38-40]. Fortin et al. (2012) and Violan et al (2014) conducted a narrative review and found various operationalisations of multimorbidity and a large variation in the prevalence of multimorbidity, particularly in studies with older adult populations or those with low socioeconomic status [38, 40]. Nguyen et al. (2019) meta-analysed the prevalence of multimorbidity across 70 studies from community settings and found that the pooled estimated prevalence was 33.1% with high levels of heterogeneity (I^2 >99%) [39]. The pooled prevalence of multimorbidity in Nguyen et al study is lower than in this study, likely because we have included studies from primary care and hospital settings (the pooled prevalence of multimorbidity in community-based studies in this analysis was 39.5%). Nguyen et al. (2019) did not carry out a meta-regression, but in narrative analysis comment that the prevalence of multimorbidity appeared higher in older adults and women [39]. Our review findings are consistent with previous literature finding that age is most important determinant of multimorbidity [5, 38, 39, 41]. While we did not find a significant difference between low and middle-income and high-income countries, Nguyen et al. in their review showed a statistically significantly higher pooled prevalence in high-income countries (the pooled prevalence from 18 studies was 37% compared to 36.8% in this review of 145 studies) than low or middle-income countries (the pooled prevalence from 31 studies was 29% compared to 44.3% in this review of 48 studies). This difference in findings may be due to the inclusion in our review of a larger number of studies from high-income or upper middle-income countries. The low number of included studies from low-income countries in this review could be explained by fewer attention paid to this relatively new research field (multimorbidity) in low-income countries and our literature search restricted to English language (proficient language of reviewers). The estimated prevalence of multimorbidity in North America was higher compared to other continents in this study despite older study populations and larger numbers of conditions found in studies from Europe. A possible explanation for the higher prevalence in North America is that private or insurance-based healthcare systems are more likely to code conditions since it affects remuneration, as well as cultural differences in relation to over-diagnosis and medicalisation [42]. On the other hand, the lower estimated multimorbidity prevalence in African studies could be attributed to the

predominance of infectious diseases and inadequate access to medical care including diagnostic services [43].

The strengths of this review are searches conducted in multiple databases, the large number of studies identified and the use of meta-analytic approaches to examine factors associated with heterogeneity of estimated multimorbidity prevalence. We examined and handled outlying studies and missing data (multiple imputation) with rigour and excluded studies that did not take into account 'healthy' populations (populations with no long-term conditions) to minimize biased estimates of multimorbidity prevalence. This review has limitations. Sensitivity analysis including all studies had similar findings with one exception, namely that sensitivity analysis found: a weaker (but still statistically significant) association with the number of conditions included in the multimorbidity measure than primary analysis. Although we examined associations with study characteristics including mean participant age, a limitation is the lack of information in the reviewed studies on prevalence estimates stratified by participant characteristics including sex, ethnicity, and socio-economic status. An additional uncontrolled factor is how studies measured multimorbidity in terms of the type (as opposed to the number) of the conditions included in measures, which varied substantially across studies with too much heterogeneity to model [13]. The exclusion of non-English studies in this review may also limit the generalisability of the research findings. Last but not least, measurement of multimorbidity is a relatively new research field and its labelling has been used variably. Thus, it is likely that not all relevant studies were identified and included in this review, but we were rigorous in our application of inclusion/exclusion criteria and did not favour adding known papers that did not appear in the search or where excluded through the process.

In spite of the methodological limitations, this review adds to our understanding of how study and measure characteristics can influence the estimated prevalence of multimorbidity. Mean age of the study population and the number of conditions included in the multimorbidity measure were the major factors associated with varying estimated prevalence of multimorbidity. A key implication is that comparing prevalence between studies requires more stratified estimates of multimorbidity prevalence. We therefore strongly recommend that as well as overall prevalence, future studies should clearly report multimorbidity prevalence stratified by age, in 5-year age bands to ensure granularity, and by sex at a minimum, and ideally by ethnicity and socio-economic status. This will allow readers to capture a more holistic picture of multimorbidity prevalence in the population

studied, and allow better comparison of prevalence in different populations, and accurate pooled estimates of prevalence in reviews.

Additionally, the number of conditions included in a measure is strongly associated with estimated multimorbidity prevalence. It would be ideal if studies additionally reported prevalence using a common core set of conditions agreed by consensus. Parallel reporting of the bespoke set chosen for the context and purpose, and a core set would improve comparability of prevalence estimates, and help identify the additional value of any bespoke multimorbidity measures. The lack of any significant difference in estimated prevalence between self-report and clinical/administrative databases in this review suggests that provided careful attention is paid to the number and type of conditions included in measures, exactly how data is collected may be less important.

To conclude, in recent years, there has been an increasing interest in the epidemiology of multimorbidity internationally. This review finds that population characteristics and measurement content are the major factors that influenced prevalence estimates of multimorbidity. Studies with older populations and larger numbers of conditions yielded a higher estimate of multimorbidity prevalence. However, heterogeneity between studies has made comparison of multimorbidity prevalence across studies difficult. To improve comparability and quality of reporting, this review suggests that future studies should use common core condition set for the measurement of multimorbidity and clearly report the prevalence of multimorbidity stratified by socio-demographics.

Contributorship statement

All authors have made substantial contributions: CMC, KN, UK, KK, RAL, JD, AA, AAL and SWM were involved in conception of the work, acquisition of funding, and critically commenting on the manuscript. IS-SH led and BG substantially contributed to the design, analysis, and interpretation of data for the review, and are responsible for the decision to submit the manuscript. IS-SH and PH screened and reviewed retrieved studies. All authors contributed to the edits of the manuscript and had access to the data. The final draft has been approved by all authors.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: we had financial support from HDRUK for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Data sharing statement

Study data are available in supplementary appendix.

Figure legends

Figure 1: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram

Figure 2: Country of origin of the included studies estimating the prevalence of multimorbidity (except studies from multiple countries)

Figure 3: Relationship between the prevalence of multimorbidity and mean age or number of conditions (the area of points is proportional to inverse variances)

Figure 4: The distribution of prevalence estimates within the subgroups of mean age and number of conditions (forest-like plot for a large review**)**

Table 1: Summary of study characteristics (Supplementary Table S8 shows the definition of variables)

Name of variable	Descriptive statistics (n=193)
Prevalence of multimorbidity (%)	Range: 2.7 to 95.6 Pooled prevalence with the REML estimator: 42.4 (38.9-46.0)
Mean age of study population (year)	Range of mean age: 32.2-83.8 Median of mean age: 62.6 (Q1, Q3: 50.1, 72.4)
No of conditions (count)	Range: 3-60 Median: 13 (Q1, Q3: 9, 19)
Country income (count, %)	
High income	145 (75.1%)
Low- or Middle-income	48 (24.9%)
Continent (count, %)	
Europe	64 (33.2%)
North America	47 (24.4%)
Asia	44 (22.8%)
Australasia	11 (5.7%)
South America	12 (6.2%)
Africa	4 (2.1%)
Multiple continents	11 (5.7%)
Study population (count, %)	
Only older people	63 (32.6%)
Middle-aged and older	46 (23.8%)
All adults	84 (43.5%)
Setting (count, %)	
Community	147 (76.2%)
Primary care	32 (16.6%)
Hospital	14 (7.3%)
Source (count, %)	
Self-report	150 (77.7%)
Database	43 (22.3%)
Risk of bias assessment (count, %)	
Low	9 (4.7%)
Moderate	162 (83.9%)
High	22 (11.4%)

IQR: Interquartile range. SD: Standard deviation. The percentages were rounded so they do not add to 100%.

Table 2: Output of meta-analytic models (n=193)

	Pooled prevalence of multimorbidity of each subgroup (%, 95% CI)	Meta-regression Unadjusted Odds Ratio (95% CI)	Meta-regression Adjusted Odds Ratio (95% CI) R^2 54.3%	FMI
Group of mean age		R^2 35.9%		
<59	28.0 (24.9-31.5)	Ref	Ref	Ref
59-73	47.6 (42.5-52.8)	2.3 (1.8-3.0)***	2.2 (1.7-2.8)***	0.3
≥74	67.0 (60.4-72.9)	5.2 (3.8-7.2)***	4.4 (3.3-5.9)***	0.2
No of conditions		R^2 19.5%		
<9	30.1 (24.9-35.7)	Ref	Ref	Ref
9-19	43.7 (39.5-48.0)	1.8 (1.3-2.5)***	1.8 (1.4-2.3)***	0.1
20-43	52.1 (43.8-60.3)	2.5 (1.7-3.7)***	2.3 (1.6-3.2)***	0.2
≥44	87.6 (81.3-92.0)	16.5 (6.4-42.6)***	8.2 (3.8-17.5)***	0.06
Setting		R^2 5.1%		
Community	39.1 (35.5-42.8)	Ref	Ref	Ref
Primary care	50.5 (39.6-61.3)	1.6 (1.1-2.3)*	1.6 (1.1-2.3)**	0.2
Hospital	59.6 (45.6-72.2)	2.3 (1.3-4.0)**	1.5 (1.0-2.4)	0.2
Source		R^2 4.0%		
Self-report	40.0 (36.2-43.8)	Ref	Ref	Ref
Database	52.7 (45.2-60.1)	1.7 (1.2-2.4)**	0.7 (0.5-1.0)	0.2
Continent		R^2 6.8%		
North America	50.4 (43.6-57.3)	Ref	Ref	Ref
Europe	44.8 (38.2-51.5)	0.8 (0.5-1.2)	0.5 (0.4-0.7)***	0.1
Australasia	35.8 (29.5-42.5)	0.5 (0.3-1.1)	0.5 (0.3-0.8)**	0.08
Asia	35.3 (29.3-42.0)	0.5 (0.4-0.8)**	0.6 (0.4-0.8)***	0.1
South America	47.5 (31.2-64.4)	0.9 (0.5-1.7)	0.8 (0.5-1.3)	0.1
Africa	13.8 (4.5-32.8)	0.2 (0.06-0.4)***	0.3 (0.1-0.6)**	0.1
Multiple continents	38.4 (29.1-48.6)	0.6 (0.3-1.2)	0.7 (0.4-1.1)	0.1
Country income		R^2 1.2%		
Low or middle-income	36.8 (29.7-44.4)	Ref		
High-income	44.3 (40.3-48.4)	1.4 (1.0-1.9)		
Study risk of bias		R^2 0.0%		
Low risk	33.3 (20.2-49.6)	Ref		
Moderate risk	42.4 (38.6-46.3)	1.5 (0.7-3.0)		
High risk	46.4 (34.1-59.1)	1.7 (0.8-3.9)		
Publication year		1.0 (1.0-1.0)		

*<0.05 **<0.01 ***<0.001

Ref: Reference category. FMI: Fraction of missing information

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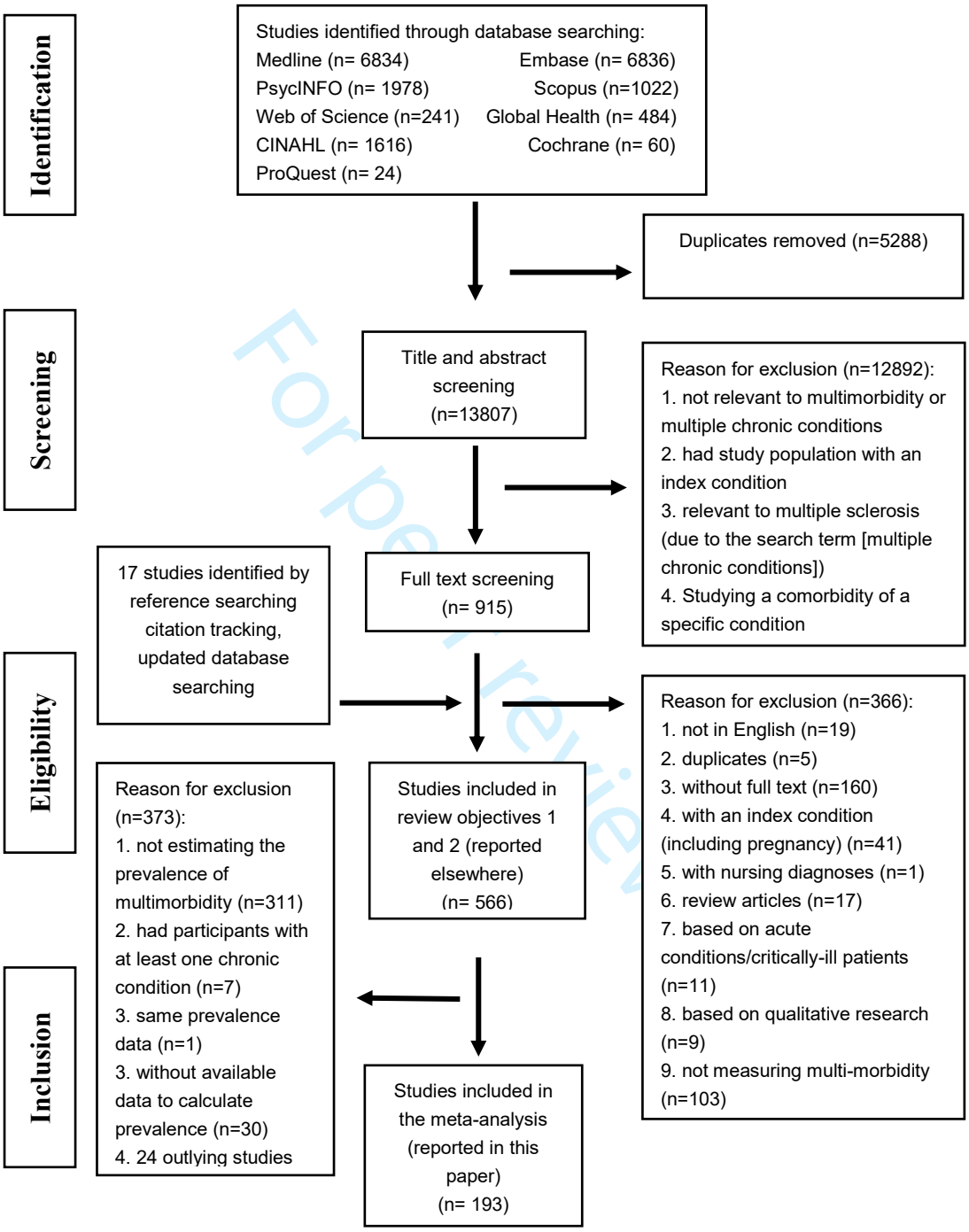
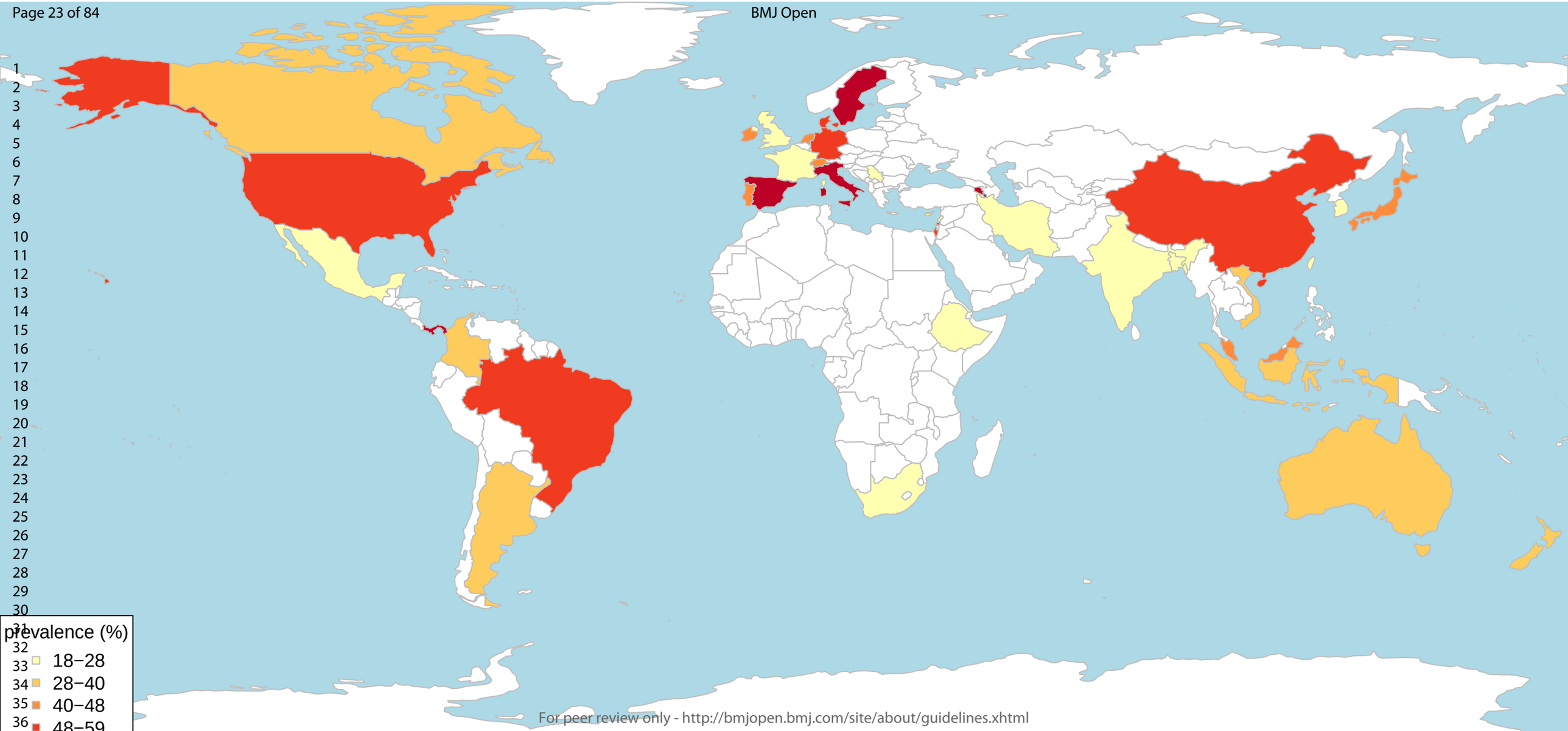
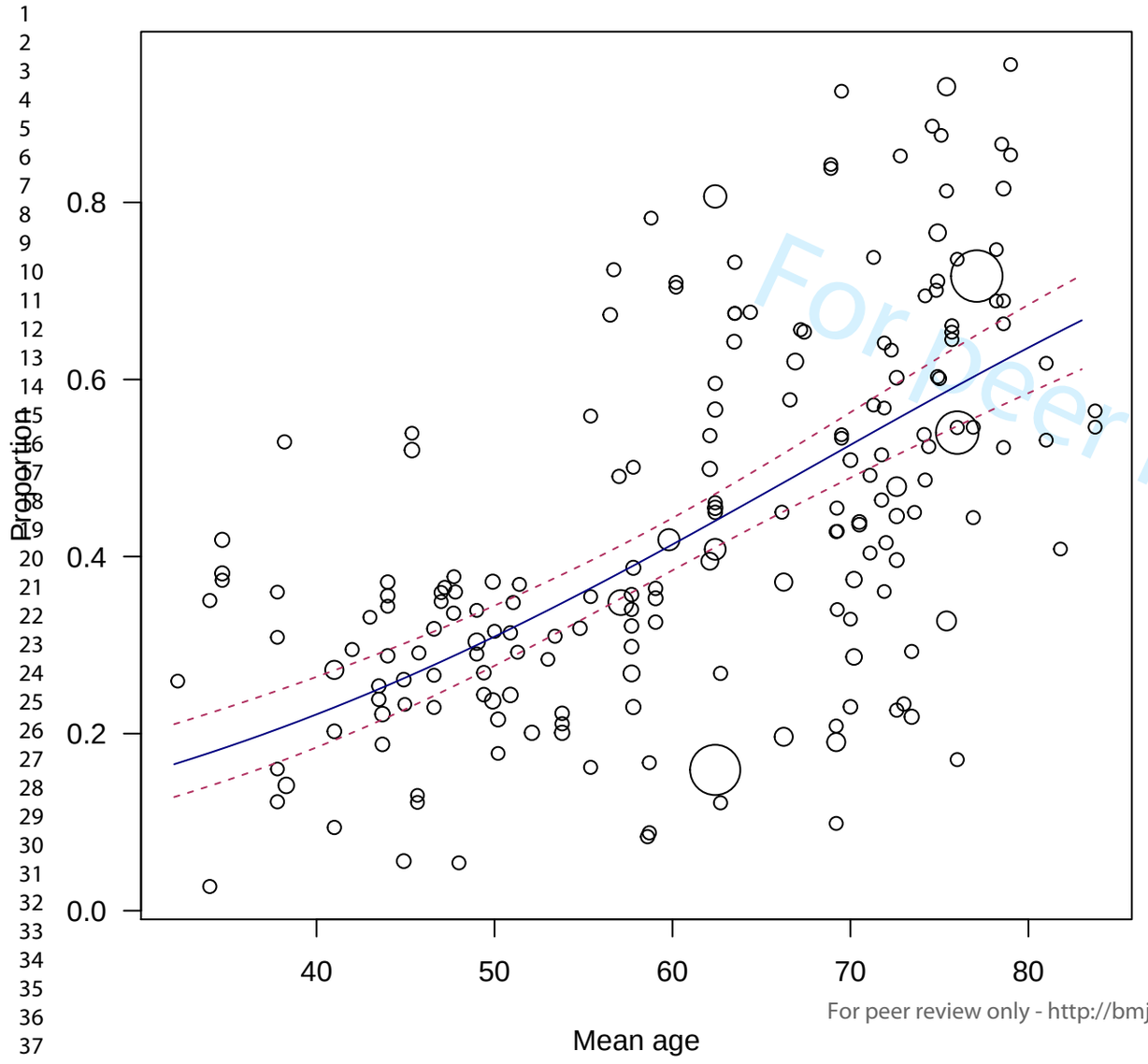
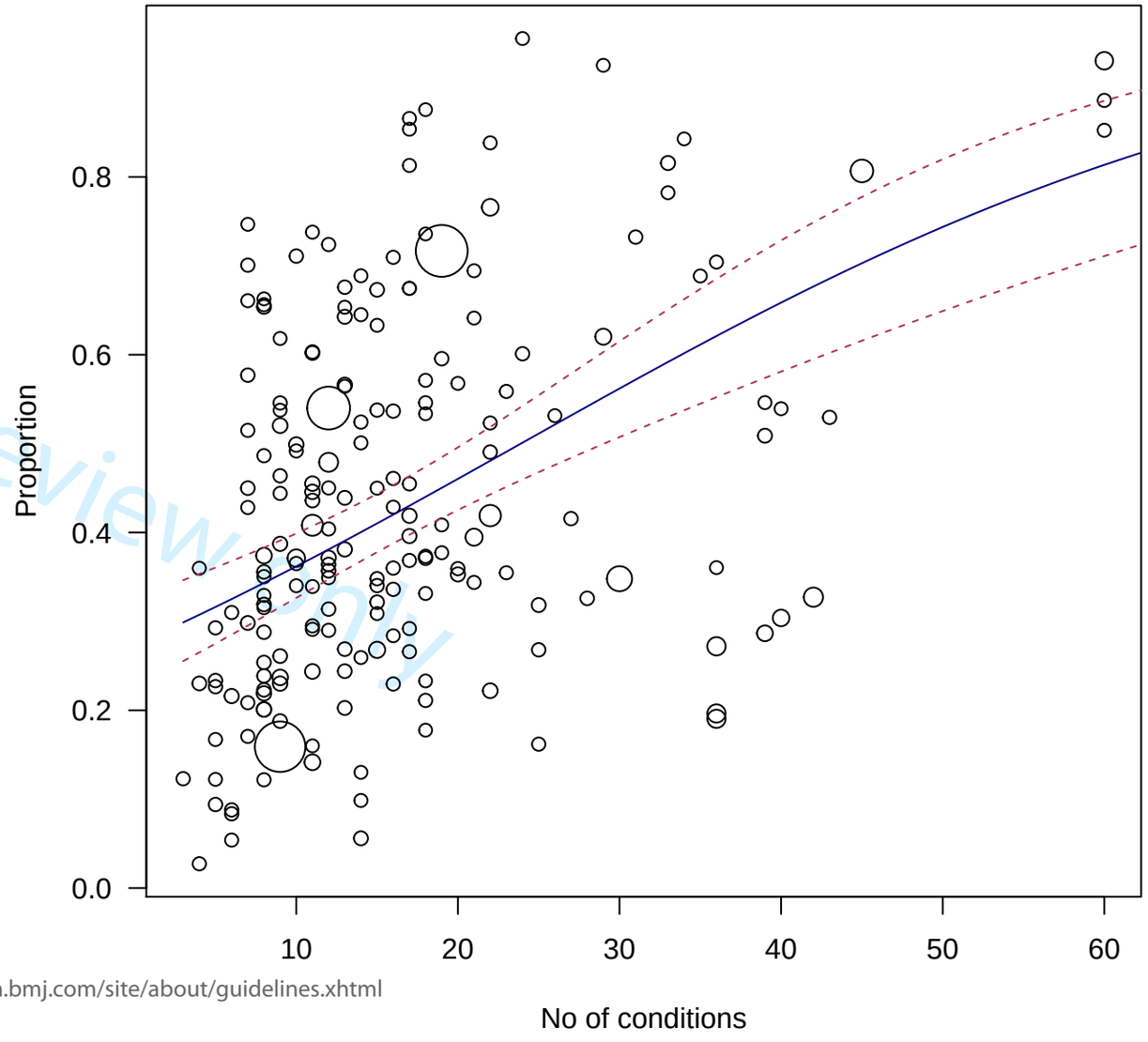
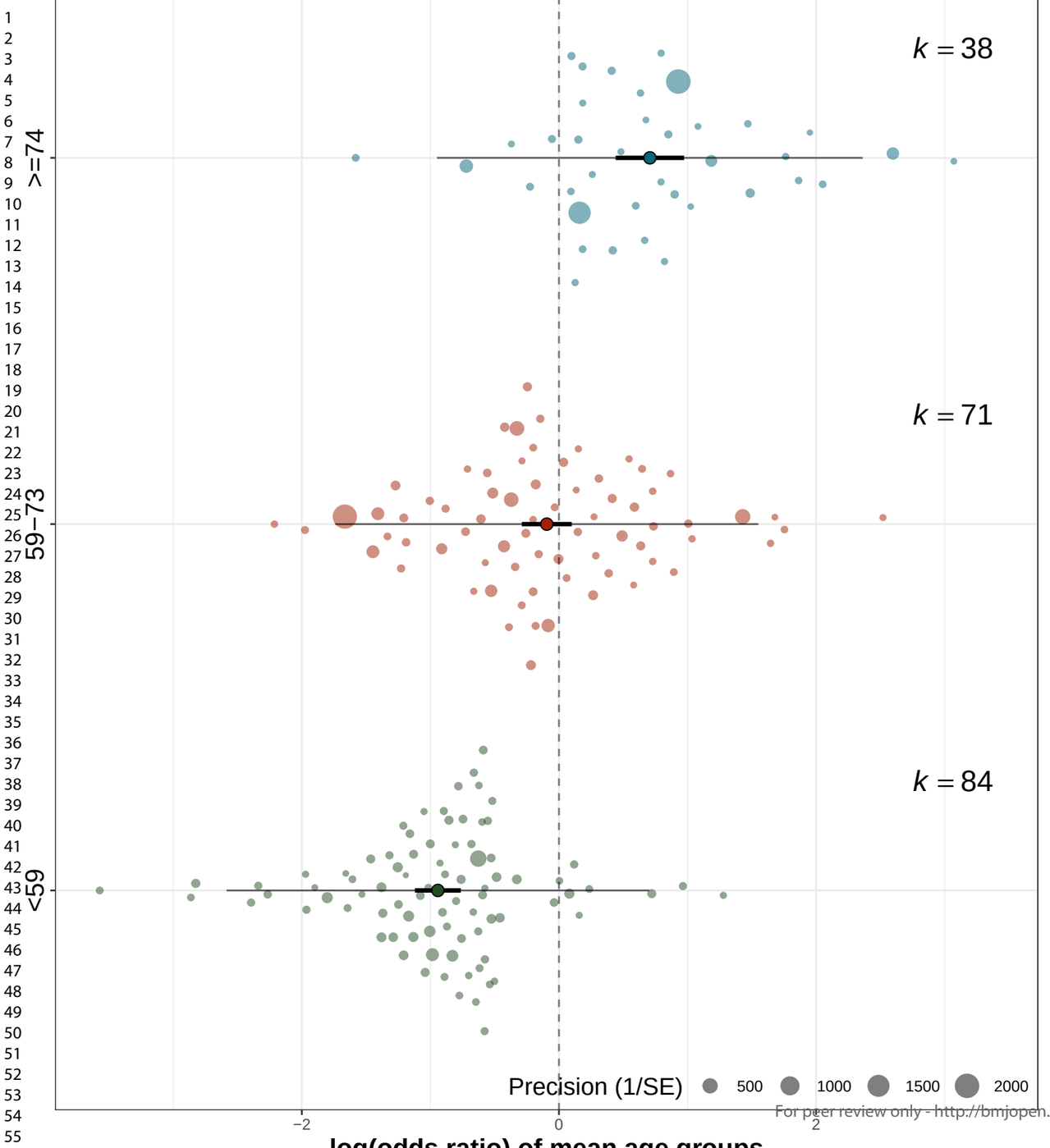
Figure 1: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram

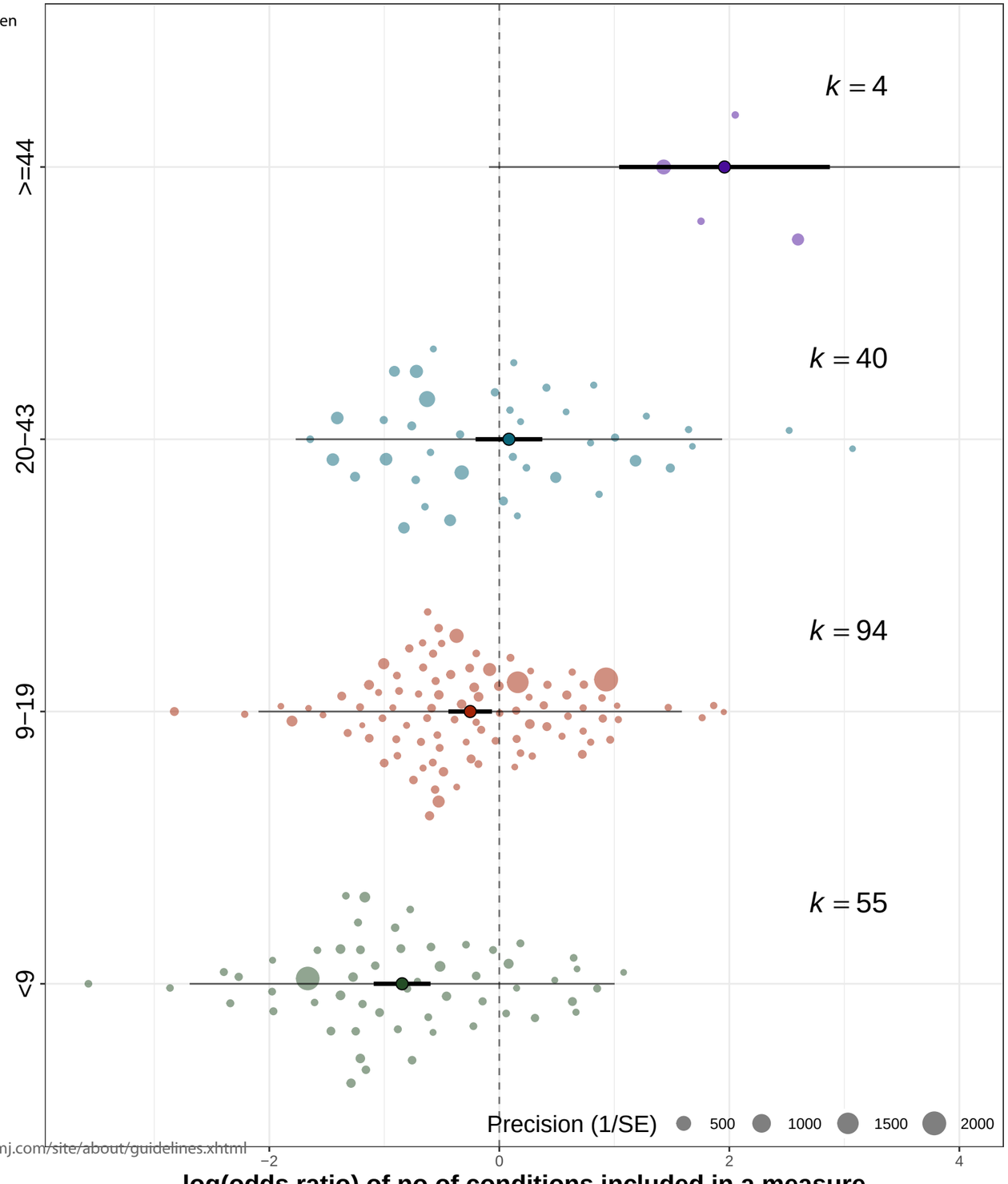












Supplementary appendix

Supplement to: Ho ISS, Azcoaga-Lorenzo A, Akbari A, et al. Variation in the estimated prevalence of multimorbidty: systematic review and meta-analysis of 193 studies.

Table of Contents

Table S1: Search strategy

Database	Search strategy
Ovid Interface PsycINFO Embase Global Health Ovid MEDLINE	1. (multimorbidit$ or multi-morbidit$ or comorbidit$ or co-morbidit$ or polymorbidit$ or poly-morbidit$ or multicondition$ or multicondition$ or "multiple chronic condition$" or "morbidity burden" or ((multiple or coexisting or co-existing or concurrent or con-current or comorbid or co-morbid) adj2 (disease$ or illness$ or condition$ or diagnos$ or morbid$))).m_titl. 2. (measure$ or index or indices or instrument$ or scale$ or "disease count$").mp. 3. 1 and 2 4. Limit 3 to human
EBSCO Interface CINAHL Plus	1. MM (multimorbidit* or multi-morbidit* or comorbidit* or co-morbidit* or polymorbidit* or poly-morbidit* or multicondition* or multicondition* or "multiple chronic condition*" or "morbidity burden" or ((multiple or coexisting or co-existing or concurrent or con-current or comorbid or co-morbid) N2 (disease* or illness* or condition* or diagnos* or morbid*))) 2. AB (measure* or index or indices or instrument* or scale*) 3. 1 AND 2 Limiters – Full Text; Human; Language: English
Scopus	TITLE (multimorbidit* or multi-morbidit* or comorbidit* or co-morbidit* or polymorbidit* or poly-morbidit* or multicondition* or multicondition* or "multiple chronic condition*" or "morbidity burden" or ((multiple or coexisting or co-existing or concurrent or con-current or morbid or co-morbid) W/2 (disease* or illness* or condition* or diagnos?s or morbid*))) AND TITLE (measure* or index or indices or instrument* or scale* or "disease counts")
Web of Science	(TI=(measure* or index or indices or instrument* or scale*))AND (TI=(multimorbidit* or multi-morbidit* or comorbidit* or co-morbidit* or polymorbidit* or poly-morbidit* or multicondition* or multicondition* or 'multiple chronic condition*' or 'morbidity burden' or ((multiple or coexisting or co-existing or concurrent or con-current or comorbid or co-morbid) NEAR/2 (disease* or illness* or condition* or diagnos* or morbid*)))) AND LANGUAGE: (English)
Cochrane library	(multimorbidity or multi-morbidity or comorbidity or co-morbidity or polymorbidity or poly-morbidity or multicondition or multicondition or 'multiple chronic conditions' or 'morbidity burden' or ((multiple or coexisting or co-existing or concurrent or con-current or comorbid or co-morbid) NEAR/2 (disease or illness or condition or diagnosis or morbid))) AND (measure or index or indices or instrument or scale or "disease count*"):ti
ProQuest Dissertations & Theses Global	ti((multimorbidit* OR multi-morbidit* OR comorbidit* OR co-morbidit* OR polymorbidit* OR poly-morbidit* OR multicondition* OR multicondition* OR 'multiple chronic condition*' OR 'morbidity burden' OR ((multiple OR coexisting OR co-existing OR concurrent OR con-current OR morbid OR co-morbid) NEAR/2 (disease* OR illness* OR condition* OR diagnos?s OR morbid*)))) AND noft((measure* OR index OR indices OR instrument* OR scale*)) Limited by: Manuscript type: Doctoral dissertations, Master's theses Language: English

Table S2: Summary of the characteristics of outlying studies

Name of variable	Outlying studies (n=24)	All studies (n=217)
Prevalence of multimorbidity (%)	Range: 7.3 to 89.1 Pooled prevalence with the REML estimator: 31.0 (21.6-42.2)	Range: 2.7-95.6 Pooled prevalence with the REML estimator: 41.1 (37.7-44.6)
Mean age of study population (year)	Range of mean age: 39.6 to 82.2 Median of mean age: 56.6 (Q1, Q3: 52.3, 66.4)	Range of mean age: 32.2 to 83.8 Median of mean age: 62.4 (Q1,Q3: 50.2,72.0)
No of conditions (count)	Range: 7 to 259 Median: 34 (Q1, Q3: 19.5, 54.5)	Range: 3 to 259 Median: 14.0 (Q1, Q3: 9, 21)
Country income (count, %)		
High income	21 (87.5%)	166 (76.5%)
Low- or Middle-income	3 (11.5%)	51 (23.5%)
Continent (count, %)		
Europe	6 (25.0%)	70 (32.3%)
North America	7 (29.2%)	54 (24.9%)
Asia	7 (29.2%)	51 (23.5%)
Australasia	3 (12.5%)	14 (6.5%)
Multiple continents	1 (4.2%)	12 (5.5%)
South America		12 (5.5%)
Africa		4 (1.8%)
Study population (count, %)		
Only older people	2 (8.3%)	65 (30.0%)
Middle-aged and older	1 (4.2%)	47 (21.7%)
All adults	15 (62.5%)	99 (45.6%)
Only children	1 (4.2%)	1 (0.5%)
All age population	5 (20.8%)	5 (2.3%)
Setting (count, %)		
Community	12 (50.0%)	159 (73.3%)
Primary care	7 (29.2%)	39 (18.0%)
Hospital	4 (16.7%)	18 (8.3%)
Care home	1 (4.2%)	1 (0.5%)
Source (count, %)		
Self-report	8 (33.3%)	158 (72.8%)
Database	16 (66.6%)	59 (27.2%)
Risk of bias assessment (count, %)		
Low	4 (16.7%)	13 (6.0%)
Moderate	19 (79.2%)	181 (83.4%)
High	1 (4.2%)	23 (10.6%)

IQR: Interquartile range. SD: Standard deviation. The percentages were rounded so they do not add up to 100%.

Table S3: Characteristics of 24 outlying studies

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias	Rationale for exclusion
[1] Stanley et al (2018)	New Zealand	Australasia	High	Hospitals	All adults	Not reported	3489747	Medical records and administrative database	61	275706	0.08	Moderate	Contributing to high levels of heterogeneity of effect sizes (Leave-one-out analysis) and the studentized residual of this study is more than 2 standard deviations away from its expected value.
[2] Lenzi et al (2016)	Italy	Europe	High	Hospitals	All adults	66.4	3759836	Medical records and administrative database	26	574208	0.15	Moderate	Contributing to high levels of heterogeneity of effect sizes (Leave-one-out analysis)
[3] Hu et al (2019)	Taiwan	Asia	High	Community	All adults	Not reported	1429527	Medical records and administrative database	20	939485	0.66	Low	Contributing to high levels of heterogeneity of effect sizes (Leave-one-out analysis)
[4] Gawron et al (2020)	USA	North America	High	Hospitals	All adults but not older people	Not reported	741612	Medical records and administrative database	Not reported	53824	0.07	Moderate	Contributing to high levels of heterogeneity of effect sizes (Leave-one-out analysis) and the studentized residual of this study is more than 2 standard deviations away from its expected value.
[5] Low et al (2019)	Singapore	Asia	High	Community	All adults	39.6	1181024	Self-report	48	309428	0.26	Low	Contributing to high levels of heterogeneity of effect sizes (Leave-one-out analysis)
[6] Wang et al (2014)	China	Asia	Low or middle	Community	Whole population	Not reported	162464	Self-report	40	17987	0.11	Low	Contributing to high levels of heterogeneity of effect sizes (Leave-one-out analysis)
[7] Gaulin et al (2019)	Canada	North America	High	Hospitals	All adults	51.2	1316832	Medical records and administrative database	34	416282	0.32	Moderate	Contributing to high levels of heterogeneity of effect sizes (Leave-one-out analysis)

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias	Rationale for exclusion
[8] Violan et al (2014)	Spain	Europe	High	Primary care	All adults	47.4	1356761	Medical records and administrative database	146	645818	0.48	Moderate	Contributing to high levels of heterogeneity of effect sizes (Leave-one-out analysis)
[9] Nicholson et al (2019)	Canada	North America	High	Primary care	All adults	52.3	367743	Medical records and administrative database	20	195838	0.53	High	Contributing to high levels of heterogeneity of effect sizes (Leave-one-out analysis)
[10] Bao et al (2019)	China	Asia	Low or middle	Community	Middle aged and older	61.36	18137	Self-report	19	3773	0.21	Moderate	Contributing to high levels of heterogeneity of effect sizes (Leave-one-out analysis)
[11] Fortin et al (2005)	Canada	North America	High	Primary care	All adults	56.55	980	Medical records and administrative database	14	873	0.89	Moderate	The studentized residual of this study is more than 2 standard deviations away from its expected value.
[12] Prazeres et al (2015)	Portugal	Europe	High	Primary care	All adults	56.3	1993	Medical records and administrative database	147	1449	0.73	Moderate	Its Mahalanobis distance exceeds the chi-squared critical value at a 0.01 significance level (multivariate outlier detection)
[13] Lawson et al (2013)	UK	Europe	High	Community	All adults	72.7	7054	Medical records and administrative database	40	1243	0.18	Moderate	Irregular patterns found in compositional data (in scatter plot and Mahalanobis distance test)- low prevalence in studies with high mean participant age and a larger number of conditions
[14] Sullivan et al (2012)	USA	North America	High	Community	All adults	Not reported	47178	Medical records and administrative database	259	19666	0.42	Moderate	Its Mahalanobis distance exceeds the chi-squared critical value at a 0.01 significance level (multivariate outlier detection)

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias	Rationale for exclusion
[15] Peng et al (2020)	China	Asia	Low or middle	Community	Only older people	71.6	1321	Self-report	15	589	0.45	Moderate	Contributing to high levels of heterogeneity of effect sizes (in leave-one-out analysis)
[16] Excoffier et al (2018)	Switzerland	Europe	High	Primary care	All adults	56.5	2904	Medical records and administrative database	75	1513	0.52	Moderate	Its Mahalanobis distance exceeds the chi-squared critical value at a 0.01 significance level (multivariate outlier detection)
[17] Chung et al (2015)	Hong Kong	Asia	High	Community	All adults	Not reported	25780	Self-report	46	3227	0.13	Moderate	Its Mahalanobis distance exceeds the chi-squared critical value at a 0.01 significance level (multivariate outlier detection)
[18] Ki et al (2017)	South Korea	Asia	High	Community	All adults	57.05	19942	Medical records and administrative database	66	5979	0.30	Moderate	Its Mahalanobis distance exceeds the chi-squared critical value at a 0.01 significance level (multivariate outlier detection)
[19] Bobo et al (2016)	USA	North America	High	Community	Whole population	Not reported	138858	Self-report	19	33682	0.24	Moderate	Infrequent values in compositional categorical data (few studies focused on whole population)
[20] Randall et al (2018)	Australia	Australasia	High	Community	Whole population	Not reported	5437018	Self-report	30	660449	0.12	Moderate	Infrequent values in compositional categorical data (few studies focused on whole population)
[21] Russell et al (2020)	New Zealand	Australasia	High	Community	Only children	Not reported	3838	Self-report	7	374	0.10	Moderate	Infrequent values in compositional categorical data (only one study focused on children population)
[22] Barnett et al (2012)	UK	Europe	High	Primary care	Whole population	Not reported	1751841	Medical records and administrative database	40	406427	0.23	Low	Infrequent values in compositional categorical data (few studies focused on whole population)

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias	Rationale for exclusion
[23] St Sauver et al (2015)	USA	North America	High	Primary care	Whole population	Not reported	106061	Medical records and administrative database	20	34592	0.33	Moderate	Infrequent values in compositional categorical data (few studies focused on whole population)
[24] Vetrano et al (2016)	Denmark, Finland, Iceland, Italy, the Netherlands, Norway, United Kingdom, Czech Republic, France, Sweden and Germany, Canada	Multiple continents	High	Care homes	Only older people	82.2	6903	Medical records and administrative database	13	5098	0.74	Moderate	Infrequent values in compositional categorical data (only one study focused on care home)

MM: Multimorbidity. No of participants: The total number of participants in the denominator for estimating prevalence in a study (which could be a subset in some included studies)

Table S4: Characteristics of 193 included studies

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[25] Aarts et al (2012)	The Netherlands	Europe	High	Primary care	All adults	55.4	1184	Medical records and administrative database	23	420	0.35	Moderate
[26] Aarts et al (2011a)	The Netherlands	Europe	High	Community	Middle aged and older	70	15188	Self-report	Not reported	7729	0.51	Moderate
[27] Aarts et al (2011b)	The Netherlands	Europe	High	Primary care	All adults	55.4	1763	Medical records and administrative database	23	985	0.56	Moderate
[28] Abizanda et al (2014)	Spain	Europe	High	Primary care	Only older people	78.6	842	Medical records and administrative database	14	580	0.69	Moderate
[29] Agborsangaya et al (2012)	Canada	North America	High	Community	All adults	46.6	4003	Self-report	16	919	0.23	Moderate
[30] Agborsangaya et al (2013)	Canada	North America	High	Community	All adults	47.8	4803	Self-report	16	1729	0.36	Moderate
[31] Agborsangaya et al (2014)	Canada	North America	High	Community	All adults	47.7	4752	Self-report	16	1597	0.34	Moderate
[32] Ahrenfeldt et al (2019)	Europe	Europe	High	Community	Middle aged and older	66.25	244258	Self-report	10	90652	0.37	Moderate
[33] Alimohammadian et al (2017)	Iran	Asia	Low or middle	Community	Middle aged and older	Not reported	49946	Self-report	8	10035	0.20	Moderate
[34] Angst et al (2002)	Switzerland	Europe	High	Primary care	All adults	Not reported	591	Medical records and administrative database	10	201	0.34	High

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[35] Appa et al (2014)	USA	North America	High	Community	All adults	60.2	1997	Self-report	16	1417	0.71	Moderate
[36] Adams et al (2017)	USA	North America	High	Community	All adults	Not reported	400000	Self-report	12	191600	0.48	Moderate
[37] Ahmadi et al (2016)	Iran	Asia	Low or middle	Community	Middle aged and older	52.1	49946	Self-report	8	10035	0.20	Moderate
[38] Amaral et al (2018)	Brazil	South America	Low or middle	Community	Only older people	Not reported	264	Self-report	8	175	0.66	Moderate
[39] An et al (2016)	South Korea	Asia	High	Community	Middle aged and older	54.8	10118	Self-report	8	3228	0.32	Moderate
[40] Araujo et al (2018)	Brazil	South America	Low or middle	Community	All adults	Not reported	4001	Self-report	12	1160	0.29	Moderate
[41] Arnold-Reed et al (2018)	Australia	Australasia	High	Primary care	All adults	38.2	4285	Medical records and administrative database	43	2269	0.53	Moderate
[42] Arokiasamy et al (2015)	6 low middle income countries (China, Ghana, India, Mexico, Russia, South Africa)	Multiple continents	Low or middle	Community	All adults	Not reported	42236	Self-report	8	9250	0.22	Moderate
[43] Sinnige et al (2015)	The Netherlands	Europe	High	Primary care	Middle aged and older	66.9	120480	Medical records and administrative database	29	74733	0.62	Moderate
[44] Zemedikun et al (2018)	UK	Europe	High	Community	Middle aged and older	Median age 58	502643	Medical records and administrative database	36	95710	0.19	Moderate
[45] Wensing et al (2001)	The Netherlands	Europe	High	Primary care	All adults	Not reported	3867	Self-report	25	626	0.16	Moderate
[46] Mounce et al (2018)	UK	Europe	High	Community	Middle aged and older	Not reported	4564	Self-report	15	1553	0.34	Moderate
[47] Taylor et al (2010)	Australia	Australasia	High	Community	All adults	Not reported	3206	Self-report	7	547	0.17	Low

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[48] Vancampfort et al (2019)	Six low and middle income countries (China, Ghana, India, Mexico, Russia, and South Africa)	Multiple continents	Low or middle	Community	Middle aged and older	62.4	34129	Self-report	11	15529	0.46	Moderate
[49] Vancampfort et al (2018)	Six low and middle income countries (China, Ghana, India, Mexico, Russia, and South Africa)	Multiple continents	Low or middle	Community	Only older people	72.6	14585	Self-report	11	8780	0.60	Moderate
[50] Aubert et al (2016)	Switzerland	Europe	High	Primary care	Middle aged and older	63.5	1002	Medical records and administrative database	17	676	0.67	Moderate
[51] Autenrieth et al (2013)	Germany	Europe	High	Community	Only older people	75.7	1007	Self-report	13	658	0.65	Moderate
[52] Bahler et al (2015)	Switzerland	Europe	High	Community	Only older people	74.9	229493	Medical records and administrative database	22	175752	0.77	Moderate
[53] Vancampfort et al (2017)	44 low and middle income countries	Multiple continents	Low or middle	Community	All adults	38.3	194431	Self-report	11	27518	0.14	Moderate
[54] Banjare et al (2014)	India	Asia	Low or middle	Community	Only older people	Not reported	310	Self-report	20	176	0.57	Moderate
[55] Barra et al (2015)	USA	North America	High	Community	All adults	45.36	43079	Self-report	Not reported	22412	0.52	Moderate
[56] Bernard et al (2016)	Australia	Australasia	High	Hospitals	Only older people	81.8	306	Medical records and administrative database	19	125	0.41	High
[57] Biswas et al (2019)	Bangladesh	Asia	Low or middle	Community	All adults	Not reported	8763	Self-report	3	1078	0.12	Moderate

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[58] Blakemore et al (2016)	UK	Europe	High	Primary care	Only older people	75	4377	Self-report	24	2631	0.60	Moderate
[59] Blyth et al (2008)	Australia	Australasia	High	Community	Only older people	76.9	1685	Self-report	18	920	0.55	Moderate
[60] Bowling et al (2019)	USA	North America	High	Community	Middle aged and older	56.7	4217	Self-report	12	3053	0.72	Moderate
[61] Britt et al (2008)	Australia	Australasia	High	Primary care	All adults	Not reported	9156	Medical records and administrative database	18	3398	0.37	Moderate
[62] Broeiro-Goncalves et al (2019)	Portugal	Europe	High	Hospitals	All adults	59.8	800376	Medical records and administrative database	22	335357	0.42	Moderate
[63] Bruce et al (2010)	Canada	North America	High	Community	All adults	37.8	453	Self-report	4	163	0.36	High
[64] Burgers et al (2010)	France, Germany, Canada, Australia, Netherlands, New Zealand, UK, USA	Multiple continents	High	Community	All adults	Not reported	8973	Self-report	7	4037	0.45	Moderate
[65] Burke et al (2017)	US, Europe, Asia	Multiple continents	High	Community	Only older people	Not reported	4668	Self-report	9	2165	0.46	Moderate
[66] Buurman et al (2016)	The Netherlands	Europe	High	Hospitals	Only older people	78.2	639	Medical records and administrative database	35	440	0.69	Moderate
[67] Calderon-Larranaga et al (2017)	Sweden	Europe	High	Primary care	Only older people	74.6	3363	Self-report	60	2980	0.89	Moderate
[68] Camargo-Casas et al (2018)	Colombia	South America	Low or middle	Community	Only older people	71.1	2000	Self-report	12	808	0.40	Moderate

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[69] Canevelli et al (2019)	Italy	Europe	High	Primary care	Only older people	75.1	185	Medical records and administrative database	18	162	0.88	High
[70] Chamberlain et al (2020)	USA	North America	High	Community	All adults	Not reported	198941	Self-report	21	78527	0.39	Low
[71] Chen et al (2018)	China	Asia	Low or middle	Community	Only older people	Not reported	30774	Medical records and administrative database	33	25101	0.82	Low
[72] Chen et al (2018)	China	Asia	Low or middle	Community	Middle aged and older	Not reported	3737	Self-report	16	1722	0.46	Moderate
[73] Cheung et al (2013)	Hong Kong (SAR of China)	Asia	High	Community	Middle aged and older	71.3	1145	Self-report	18	654	0.57	Moderate
[74] Chu et al (2018)	Hong Kong (SAR of China)	Asia	High	Primary care	Middle aged and older	Not reported	382	Medical records and administrative database	40	206	0.54	Moderate
[75] Chudasama et al (2019)	UK	Europe	High	Community	Middle aged and older	Median age:58	491939	Medical records and administrative database	36	96622	0.20	Moderate
[76] Cimarras-Otal et al (2014)	Spain	Europe	High	Community	All adults	Not reported	22190	Self-report	20	7830	0.35	Moderate
[77] Chin et al (2016)	Hong Kong (SAR of China)	Asia	High	Primary care	All adults	Median age: 48	9259	Self-report	8	2350	0.25	Moderate
[78] Agrawal et al (2016)	India, China, Russia, Mexico, South Africa, Ghana	Multiple continents	Low or middle	Community	All adults	57.8	40166	Self-report	9	9238	0.23	Moderate
[79] Gu et al (2018)	China	Asia	Low or middle	Community	Only older people	Not reported	411	Self-report	13	232	0.56	Moderate
[80] Gunn et al (2012)	Australia	Australasia	High	Primary care	All adults	50.89	6864	Self-report	12	2154	0.31	Moderate

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[81] Han et al (2013)	USA	North America	High	Primary care	Only older people	76	159	Medical records and administrative database	18	117	0.74	High
[82] Hanlon et al (2018)	UK	Europe	High	Community	All adults	Not reported	493737	Medical records and administrative database	42	161576	0.33	Low
[83] Jantsch et al (2018)	Brazil	South America	Low or middle	Community	All adults	42	3092	Self-report	11	912	0.29	Moderate
[84] John et al (2003)	USA	North America	High	Community	Only older people	71.3	992	Self-report	11	732	0.74	High
[85] Johnson-Lawrence et al (2017)	USA	North America	High	Community	All adults	49.9	115097	Self-report	9	27278	0.24	Moderate
[86] Johnston et al (2019)	UK	Europe	High	Community	All adults	48	7184	Self-report	Not reported	388	0.05	Moderate
[87] Jones et al (2016)	USA	North America	High	Community	Only older people	Not reported	6964	Self-report	10	4951	0.71	Moderate
[88] Jovic et al (2016)	Serbia	Europe	Low or middle	Community	All adults	49.4	13103	Self-report	13	3522	0.27	Moderate
[89] Juul-Larsen et al (2020)	Denmark	Europe	High	Hospitals	Only older people	Median age: 78	369	Self-report	34	311	0.84	Moderate
[90] Hudon et al (2008)	Canada	North America	High	Community	All adults	Not reported	16782	Self-report	25	5343	0.32	Low
[91] Hussain et al (2015)	Indonesia	Asia	Low or middle	Community	Middle aged and older	Not reported	9438	Self-report	12	3369	0.36	Moderate
[92] Ie et al (2017)	USA	North America	High	Hospitals	Only older people	Not reported	1084	Medical records and administrative database	24	1036	0.96	High
[93] Ishizaki et al (2019)	Japan	Asia	High	Community	Only older people	76.9	2525	Self-report	9	1121	0.44	Moderate

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[94] Danon-Hersch et al (2012)	Switzerland	Europe	High	Community	Only older people	Not reported	1283	Self-report	12	448	0.35	Moderate
[95] de Heer et al (2013)	USA	North America	High	Community	All adults	47.72	1002	Self-report	19	378	0.38	Moderate
[96] Demirchyan et al (2013)	Armenia	Asia	Low or middle	Community	All adults	58.8	721	Self-report	Not reported	564	0.78	High
[97] Fabbri et al (2015)	Italy	Europe	High	Community	Only older people	73.6	1018	Self-report	15	458	0.45	Moderate
[98] Fillenbaum et al (2000)	USA	North America	High	Community	Only older people	73.44	4034	Self-report	5	1181	0.29	Moderate
[99] Kaneko et al (2019)	Japan	Asia	High	Community	Only older people	Not reported	253	Self-report	Not reported	135	0.53	Moderate
[100] Kang et al (2017)	South Korea	Asia	High	Primary care	All adults	32.2	590	Medical records and administrative database	14	153	0.26	Moderate
[101] Gandhi et al (2020)	USA	North America	High	Community	All adults	Not reported	9499	Self-report	8	3379	0.36	Moderate
[102] Costa et al (2018)	Brazil	South America	Low or middle	Community	Only older people	Not reported	1451	Self-report	29	1343	0.93	Moderate
[103] Rizzuto et al (2017)	Sweden	Europe	High	Community	Only older people	Not reported	1099	Self-report	36	774	0.70	Moderate
[104] Dhalwani et al (2017)	UK	Europe	High	Community	Middle aged and older	Not reported	5476	Self-report	18	1156	0.21	Moderate
[105] Elixhauser et al (1998)	USA	North America	High	Hospitals	All adults	57.1	1779167	Medical records and administrative database	30	619150	0.35	Low
[106] Fabbri et al (2015)	USA	North America	High	Hospitals	Only older people	72.3	695	Self-report	15	440	0.63	Moderate

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[107] Fortin et al (2014)	Canada	North America	High	Community	Middle aged and older	57.8	1196	Self-report	14	599	0.50	Moderate
[108] Fuchs et al (1998)	Israel	Asia	High	Community	Only older people	Not reported	1820	Self-report	14	1174	0.65	Moderate
[109] Galenkamp et al (2011)	The Netherlands	Europe	High	Community	Middle aged and older	69.2	2046	Self-report	7	876	0.43	High
[110] Galenkamp et al (2016)	Germany, UK, Italy, The Netherlands, Spain and Sweden	Europe	High	Community	Only older people	74.2	2792	Self-report	8	1358	0.49	Moderate
[111] Gamma et al (2001)	Switzerland	Europe	High	Community	All adults	Not reported	407	Self-report	14	53	0.13	High
[112] Ge et al (2018)	Singapore	Asia	High	Community	All adults	51.4	1940	Self-report	17	715	0.37	Moderate
[113] Ge et al (2019)	Singapore	Asia	High	Community	All adults	51.3	1932	Self-report	17	564	0.29	Moderate
[114] Gould et al (2016)	USA	North America	High	Community	Only older people	74.82	4184	Self-report	7	2932	0.70	Moderate
[115] Habib et al (2014)	Lebanon	Asia	Low or middle	Community	All adults	46.6	2501	Self-report	Not reported	665	0.27	Moderate
[116] Harrison et al (2017)	Australia	Australasia	High	Primary care	All adults	Not reported	8707	Medical records and administrative database	28	2838	0.33	Moderate
[117] Hayek et al (2017)	Israel	Asia	High	Community	All adults	47.2	4325	Self-report	10	1579	0.37	Moderate
[118] Henninger et al (2012)	USA	North America	High	Community	Only older people	76	3212	Self-report	9	1753	0.55	Moderate
[119] Hernandez et al (2019)	Ireland	Europe	High	Community	Middle aged and older	Not reported	6101	Self-report	31	4468	0.73	Moderate

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[120] Ho et al (2014)	Singapore	Asia	High	Community	Middle aged and older	66.15	1844	Self-report	12	830	0.45	Moderate
[121] Khan et al (2019)	Bangladesh	Asia	Low or middle	Community	All adults	58.6	12338	Self-report	6	1031	0.08	Low
[122] Kiliari et al (2013)	Cyprus	Europe	High	Community	All adults	53	465	Self-report	Not reported	132	0.28	Moderate
[123] King et al (2018)	USA	North America	High	Community	All adults	Not reported	5541	Self-report	11	3342	0.60	Moderate
[124] Kingston et al (2018)	UK	Europe	High	Community	All adults	Not reported	9723900	Self-report	12	5250906	0.54	High
[125] Koyanagi et al (2018)	China, Ghana, India, Mexico, Russia, and South Africa	Multiple continents	Low or middle	Community	Middle aged and older	62.1	32715	Self-report	10	16324	0.50	Moderate
[126] Kriegsman et al (2004)	The Netherlands	Europe	High	Community	Middle aged and older	69.2	2489	Self-report	7	519	0.21	Moderate
[127] Kristensen et al (2019)	Germany	Europe	High	Community	Middle aged and older	63.47	19605	Self-report	13	12600	0.64	Moderate
[128] Kristensen et al (2019)	Germany	Europe	High	Community	Middle aged and older	64.37	7604	Self-report	13	5140	0.68	Moderate
[129] Kunna et al (2017)	China, Ghana	Multiple continents	Low or middle	Community	Middle aged and older	Not reported	15864	Self-report	7	4731	0.30	Low
[130] Kuwornu et al (2014)	Canada	North America	High	Community	All adults	51.05	3284	Self-report	15	1143	0.35	Moderate
[131] Lai et al (2019)	Hong Kong (SAR of China)	Asia	High	Community	All adults	Not reported	69636	Self-report	14	3898	0.06	Moderate
[132] Lai et al (2018)	Hong Kong (SAR of China)	Asia	High	Community	All adults	Not reported	300	Self-report	11	48	0.16	Moderate
[133] Laires et al (2019)	Portugal	Europe	High	Community	All adults	Not reported	15196	Self-report	13	6671	0.44	Moderate

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[134] Lang et al (2015)	USA	North America	High	Community	Middle aged and older	53.4	3058	Self-report	6	948	0.31	Moderate
[135] Le Cossec et al (2016)	France	Europe	High	Community	Middle aged and older	70	15325	Self-report	4	3528	0.23	Moderate
[136] Lee et al (2007)	USA	North America	High	Hospitals	Middle aged and older	Not reported	741847	Medical records and administrative database	11	302792	0.41	Low
[137] Lee et al (2018)	Taiwan	Asia	High	Community	Only older people	Not reported	20898	Medical records and administrative database	Not reported	4234	0.20	High
[138] Li et al (2016)	UK	Europe	High	Primary care	All adults	Not reported	27806	Self-report	12	10332	0.37	Moderate
[139] Li et al (2019)	USA	North America	High	Community	Middle aged and older	67.4	14996	Self-report	8	9805	0.65	Moderate
[140] Lujic et al (2017)	Australia	Australasia	High	Community	Middle aged and older	70.2	90352	Self-report	8	33792	0.37	Moderate
[141] Lupianez-Villanueva et al (2018)	14 European countries	Europe	High	Community	All adults	Not reported	14000	Self-report	13	3416	0.24	Moderate
[142] Zhou et al (2018)	Bangladesh, India and China	Asia	Low or middle	Community	All adults	Not reported	18696	Self-report	9	3512	0.19	Moderate
[143] Zhang et al (2019)	China	Asia	Low or middle	Community	Only older people	70.5	11707	Self-report	11	5104	0.44	Moderate
[144] Wong et al (2010)	Canada	North America	High	Community	Only older people	Not reported	740	Self-report	7	489	0.66	Moderate
[145] Weimann et al (2016)	South Africa	Africa	Low or middle	Community	All adults	34	18526	Self-report	4	506	0.027	Moderate
[146] Wang et al (2017)	Australia	Australasia	High	Community	All adults	44	8820	Self-report	8	2539	0.29	Moderate
[147] Wang et al (2019)	South Africa	Africa	Low or middle	Community	Only older people	Not reported	2627	Self-report	5	439	0.17	Moderate

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[148] Wade et al (2019)	New Zealand	Australasia	High	Community	All adults	59.05	7654	Self-report	12	2786	0.36	Moderate
[149] Maciejewski et al (2019)	USA	North America	High	Community	Only older people	77.1	20124230	Medical records and administrative database	19	14425446	0.72	Moderate
[150] Marengoni et al (2016)	Sweden	Europe	High	Community	Only older people	74.4	3155	Medical records and administrative database	14	1654	0.52	Moderate
[151] Marengoni et al (2009)	Sweden	Europe	High	Community	Only older people	Not reported	1099	Self-report	22	575	0.52	Moderate
[152] Marques et al (2018)	13 European countries	Europe	High	Community	All adults	50.2	32931	Self-report	6	7113	0.22	Moderate
[153] Mavaddat et al (2014)	UK	Europe	High	Primary care	Middle aged and older	58.7	11439	Self-report	6	1006	0.09	Moderate
[154] McDaid et al (2013)	Ireland	Europe	High	Community	Middle aged and older	Not reported	6018	Self-report	8	733	0.12	High
[155] Melis et al (2014)	Sweden	Europe	High	Hospitals	Only older people	83.75	390	Medical records and administrative database	39	213	0.55	Moderate
[156] Min et al (2007)	USA	North America	High	Community	Only older people	81	372	Self-report	9	230	0.62	High
[157] Momtaz et al (2010)	Malaysia	Asia	High	Community	Only older people	69.26	385	Self-report	16	165	0.43	Moderate
[158] Mondor et al (2018)	Canada	North America	High	Community	All adults	Not reported	27195	Medical records and administrative database	17	11390	0.42	Moderate
[159] Muggah et al (2012)	Canada	North America	High	Community	All adults	Not reported	28450000	Medical records and administrative database	9	4523550	0.16	Moderate
[160] Nagel et al (2008)	Germany	Europe	High	Community	Middle aged and older	56.5	13781	Self-report	15	9275	0.67	Moderate

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[161] Niedzwiedz et al (2019)	USA	North America	High	Community	Middle aged and older	67.2	2272	Self-report	8	1491	0.66	Moderate
[162] Nunes et al (2016)	Brazil	South America	Low or middle	Community	All adults	45.75	2927	Self-report	11	852	0.29	Moderate
[163] Nunes et al (2017)	Brazil	South America	Low or middle	Community	All adults	43.7	60202	Self-report	22	13365	0.22	Moderate
[164] Nunes et al (2015)	Brazil	South America	Low or middle	Community	Only older people	Not reported	1593	Self-report	17	1295	0.81	Moderate
[165] Olaya et al (2017)	Spain	Europe	High	Community	Only older people	71.75	2113	Self-report	7	1088	0.51	Moderate
[166] Olivares et al (2017)	Argentina	South America	High	Community	All adults	43	1044	Self-report	Not reported	346	0.33	Moderate
[167] Park et al (2018)	South Korea	Asia	High	Community	Middle aged and older	62.7	5996	Self-report	25	1607	0.27	Moderate
[168] Patel et al (2006)	Mexico	South America	Low or middle	Community	Middle aged and older	73	7852	Self-report	5	1833	0.23	Moderate
[169] Pati et al (2016)	India	Asia	Low or middle	Community	All adults	44.96	103	Self-report	18	24	0.23	Moderate
[170] Pati et al (2019)	India	Asia	Low or middle	Primary care	All adults	44	1649	Self-report	21	567	0.34	Moderate
[171] Payne et al (2013)	UK	Europe	High	Primary care	All adults	49	180815	Medical records and administrative database	40	54945	0.30	Moderate
[172] Perez et al (2020)	Sweden	Europe	High	Community	Only older people	72.8	2596	Self-report	60	2213	0.85	Moderate
[173] Petersen et al (2019)	South Africa	Africa	Low or middle	Primary care	All adults	Not reported	2549	Self-report	Not reported	893	0.35	Moderate
[174] Pfortmueller et al (2013)	Switzerland	Europe	High	Hospitals	All adults	Median age: 28	3170	Medical records and administrative database	18	1183	0.37	High

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[175] Pressley et al (1999)	USA	North America	High	Hospitals	Only older people	Not reported	5934	Medical records and administrative database	Not reported	3534	0.60	Moderate
[176] Prior et al (2016)	Denmark	Europe	High	Community	All adults	Not reported	118410	Self-report	39	33937	0.29	Moderate
[177] Ribeiro et al (2018)	Brazil	South America	High	Community	Only older people	70	820	Self-report	8	270	0.33	Moderate
[178] Ruel et al (2014)	Australia	Australasia	High	Community	All adults	50	1854	Self-report	8	585	0.32	Moderate
[179] Ruel et al (2014)	China	Asia	Lor or middle	Community	All adults	49	1020	Self-report	11	346	0.34	Moderate
[180] Ryan et al (2018)	Ireland	Europe	High	Community	Middle aged and older	Not reported	4823	Self-report	16	2588	0.54	Moderate
[181] Schmidt et al (2016)	Austria, Belgium, Denmark, France, Germany, Italy, the Netherlands, Spain, Sweden, and Switzerland	Europe	High	Community	Only older people	Not reported	56609	Self-report	11	13794	0.24	Moderate
[182] Schottker et al (2016)	Germany	Europe	High	Primary care	Middle aged and older	Median age:70	2547	Medical records and administrative database	14	251	0.10	Moderate
[183] Seo et al (2017)	South Korea	Asia	High	Community	Middle aged and older	Not reported	156747	Self-report	15	42006	0.27	Moderate
[184] She et al (2019)	China	Asia	Low or middle	Hospitals	Only older people	68.9	1497	Self-report	22	1255	0.84	Moderate
[185] Singh et al (2019)	India	Asia	Low or middle	Community	All adults	41	16287	Self-report	5	1531	0.09	Moderate
[186] Stepanova et al (2015)	USA	North America	High	Community	All adults	34.7	26225	Self-report	13	9992	0.38	High
[187] Stickley et al (2020)	USA	North America	High	Community	All adults	44.9	15311	Self-report	9	3996	0.26	High

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[188] Streit et al (2014)	Switzerland	Europe	High	Primary care	Middle aged and older	63.5	1002	Medical records and administrative database	17	676	0.67	Moderate
[189] Stubbs et al (2018)	China, Ghana, India, Mexico, Russia, South Africa	Multiple continents	Low or middle	Community	Middle aged and older	62.4	34129	Self-report	13	19317	0.57	Moderate
[190] Su et al (2016)	China	Asia	Low or middle	Community	Only older people	Not reported	2058	Self-report	10	1012	0.49	Moderate
[191] Sundstrup et al (2017)	USA	North America	High	Community	All adults	43.5	10427	Self-report	8	2489	0.24	High
[192] Takahashi et al (2016)	USA	North America	High	Hospitals	All adults	57	6402	Medical records and administrative database	Not reported	3140	0.49	High
[193] Tinetti et al (2011)	USA	North America	High	Community	Only older people	72.6	5298	Self-report	5	1200	0.23	High
[194] Troelstra et al (2020)	The Netherlands	Europe	High	Community	All adults	Not reported	604	Self-report	26	321	0.53	High
[195] van Zon et al (2020)	USA	North America	High	Community	Middle aged and older	53.8	10719	Self-report	8	2390	0.22	Moderate
[196] Vancampfort et al (2017)	China, Ghana, India, Mexico, Russia, and South Africa	Multiple continents	Low or middle	Community	All adults	Median age: 62	32585	Self-report	11	14524	0.45	Moderate
[197] Vassilaki et al (2015)	USA	North America	High	Primary care	Only older people	78.5	2176	Medical records and administrative database	17	1884	0.87	Moderate
[198] Vassilaki et al (2016)	USA	North America	High	Primary care	Only older people	79	1449	Medical records and administrative database	17	1237	0.85	Moderate
[199] Villarreal et al (2015)	Panama	South America	High	Primary care	Only older people	78.2	304	Self-report	7	227	0.75	Moderate
[200] Violan et al (2019)	Spain	Europe	High	Primary care	Only older people	75.4	916619	Medical records and	60	853085	0.93	Moderate

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
								administrative database				
[201] von Strauss et al (2000)	Sweden	Europe	High	Community	Only older people	Not reported	502	Self-report	15	155	0.31	Moderate
[202] Vos et al (2013)	The Netherlands	Europe	High	Community	Only older people	71.9	315	Self-report	21	202	0.64	Moderate
[203] Vu et al (2019)	Vietnam	Asia	Low or middle	Hospitals	Only older people	71.9	405	Medical records and administrative database	Not reported	146	0.36	High
[204] Wang et al (2018)	USA	North America	High	Community	All adults	47	3086	Self-report	20	1109	0.36	Moderate
[205] Wang et al (2017)	China	Asia	Low or middle	Community	Only older people	69.24	2705	Self-report	17	1230	0.45	Moderate
[206] Wijers et al (2019)	Spain	Europe	High	Community	Middle aged and older	74.2	707	Self-report	21	491	0.69	Moderate
[207] Williams et al (2016)	USA	North America	High	Community	All adults	Not reported	23789	Self-report	9	9213	0.39	Moderate
[208] Woldesemayat et al (2018)	Ethiopia	Africa	Low or middle	Primary care	All adults	Not reported	411	Self-report	18	73	0.18	Moderate
[209] Yao et al (2020)	China	Asia	Low or middle	Community	Middle aged and older	57.7	10084	Self-report	15	3243	0.32	Moderate
[210] Yorke et al (2017)	USA	North America	High	Community	Middle aged and older	66.6	5877	Self-report	7	3391	0.58	Moderate
[211] You et al (2019)	China	Asia	Low or middle	Community	Only older people	72	5296	Self-report	27	2201	0.42	Moderate
[212] Zhang et al (2020)	China	Asia	Low or middle	Community	Only older people	74.14	4348	Self-report	15	2338	0.54	Moderate
[213] Khanam et al (2011)	Bangladesh	Asia	Low or middle	Community	Only older people	69.5	452	Medical records and administrative database	9	243	0.54	Moderate

Author	Country	Continent	Country income	Setting	Study population	Mean age	No of participants	Source	No of conditions measured	No of MM cases	Proportion with MM	Risk of bias
[214] Cornell et al (2009)	USA	North America	High	Primary care	All adults	62.4	1645314	Medical records and administrative database	45	1327382	0.81	Moderate
[215] Cassell et al (2018)	UK	Europe	High	Primary care	All adults	Not reported	403985	Medical records and administrative database	36	109884	0.27	Moderate
[216] Wong et al (2019)	Hong Kong (SAR of China)	Asia	High	Community	All adults	45.67	1014	Self-report	5	124	0.12	Moderate
[217] Puth et al (2017)	Germany	Europe	High	Community	All adults	Not reported	19294	Self-report	17	7640	0.40	Moderate

MM: Multimorbidity. No of participants is the total number of participants in the denominator for estimating prevalence in a study (which could be a subset in some included studies)

Table S5: Associations between predictors

	Mean age (lm) Unadjusted coefficient estimates	**No of conditions (nb) Unadjusted incident rate ratio**
Mean age		1·0 (1.0-1.0)
Source		
Self-report	59.7 (57.1-62.3) (intercept)	Ref
Database	7.0 (1.5-12.5)*	1.8 (1.5-2.2)***
Continent		
Europe	66.8 (62.8-70.9) (intercept)	Ref
North America	-7.0 (-12.8 to -1.1)*	0.6 (0.5-0.8)***
Australasia	-8.0 (-17.5-1.6)	0.8 (0.6-1.1)
Asia	-8.4 (-14.6 to -2.2)**	0.6 (0.5-0.8)***
South America	-8.5 (-18.0-1.1)	0.6 (0.4-0.9)**
Africa	-32.8 (-57.8 to -8.0)**	0.4 (0.2-0.8)*
Multiple continents	-7.6 (-18.3-3.2)	0.5 (0.3-0.7)***
Setting		
Community	59.8 (57.2-62.5) (intercept)	Ref
Primary care	3.5 (-2.5-9.6)	1.7 (1.4-2.1)***
Hospitals	10.2 (1.5-19.0)*	1.8 (1.3-2.4)***
Study population		
All adults	48.3 (46.6-50.0) (intercept)	Ref
Middle-aged and older	15.4 (12.7-18.0)***	0.9 (0.7-1.1)
Only older people	26.2 (23.7-28.7)***	1.2 (0.9-1.4)

*<0.05 **<0.01 ***<0.001

Ref: Reference category. lm: Linear regression. nb: Negative binomial regression

Table S6: Risk of bias assessment of included studies

Author	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Publication bias	Conflict of interest	Overall rating	Reporting of MM measure and definition
[25.] Aarts et al (2012)	Moderate	Moderate	Moderate	High	Low	Low	Moderate	Low	Moderate	Yes
[26.] Aarts et al (2011)	Low	High	Moderate	High	Moderate	Moderate	Moderate	Low	Moderate	No
[27.] Aarts et al (2011)	Moderate	Moderate	Moderate	High	Low	Low	Moderate	Low	Moderate	Yes
[28.] Abizanda et al (2014)	Moderate	Moderate	Moderate	High	Moderate	Moderate	Moderate	Low	Moderate	Yes
[29.] Agborsangaya et al (2012)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[30.] Agborsangaya et al (2013)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[31.] Agborsangaya et al (2014)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[32.] Ahrenfeldt et al (2019)	Low	Moderate	Moderate	High	Low	High	Moderate	Low	Moderate	No
[33.] Alimohammadian et al (2017)	Low	Moderate	Moderate	High	Low	High	Moderate	Low	Moderate	Yes
[34.] Angst et al (2002)	Moderate	Moderate	Moderate	High	Low	High	High	Unclear	High	No
[35.] Appa et al (2014)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[36.] Adams et al (2017)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[37.] Ahmadi et al (2016)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[38.] Amaral et al (2018)	High	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes

Author	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Publication bias	Conflict of interest	Overall rating	Reporting of MM measure and definition
[39.] An et al (2016)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[40.] Araujo et al (2018)	Low	Moderate	Low	High	Moderate	High	Moderate	Low	Moderate	Yes
[41.] Arnold-Reed et al (2018)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[42.] Arokiasamy et al (2015)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[43.] Sinnige et al (2015)	Low	Moderate	Moderate	High	Low	Low	Moderate	Low	Moderate	Yes
[44.] Zemedikun et al (2018)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[45.] Wensing et al (2001)	Moderate	Moderate	Moderate	High	Moderate	Moderate	Moderate	Unclear	Moderate	Yes
[46.] Mounce et al (2018)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[47.] Taylor et al (2010)	Low	Moderate	Moderate	High	Low	Low	Moderate	Low	Low	Yes
[48.] Vancampfort et al (2019)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[49.] Vancampfort et al (2018)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[50.] Aubert et al (2016)	Moderate	Moderate	Moderate	High	Moderate	Low	Moderate	Low	Moderate	Yes
[51.] Autenrieth et al (2013)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[52.] Bahler et al (2015)	Low	Moderate	Moderate	High	Moderate	Low	Moderate	Low	Moderate	Yes
[53.] Vancampfort et al (2017)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes

Author	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Publication bias	Conflict of interest	Overall rating	Reporting of MM measure and definition
[54.] Banjare et al (2014)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[55.] Barra et al (2015)	Moderate	Moderate	High	High	Moderate	High	Moderate	Unclear	Moderate	No
[56.] Bernard et al (2016)	High	Moderate	High	High	Moderate	Low	Moderate	Low	High	No
[57.] Biswas et al (2019)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	No
[58.] Blakemore et al (2016)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	No
[59.] Blyth et al (2008)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[60.] Bowling et al (2019)	Low	Moderate	Moderate	High	Moderate	Low	Moderate	Low	Moderate	Yes
[61.] Britt et al (2008)	Low	Moderate	High	High	Moderate	Moderate	Moderate	Low	Moderate	Yes
[62.] Broeiro-Goncalves (2019)	Low	Moderate	High	High	Moderate	Moderate	Moderate	Low	Moderate	Yes
[63.] Bruce et al (2010)	High	Moderate	Moderate	High	Low	High	Moderate	Unclear	High	No
[64.] Burgers et al (2010)	Low	Moderate	High	High	Moderate	Low	Moderate	Low	Moderate	Yes
[65.] Burke et al (2017)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[66.] Buurman et al (2016)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[67.] Calderon-Larranaga et al (2017)	Moderate	Moderate	Moderate	High	Low	Low	Moderate	Low	Moderate	Yes
[68.] Camargo-Casas et al (2018)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes

Author	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Publication bias	Conflict of interest	Overall rating	Reporting of MM measure and definition
[69.] Canevelli et al (2019)	High	High	High	High	Moderate	High	Moderate	Low	High	Yes
[70.] Chamberlain et al (2020)	Low	Moderate	Moderate	High	Low	Low	Moderate	Low	Low	Yes
[71.] Chen et al (2018)	Low	Moderate	High	High	Low	Low	Moderate	Low	Low	Yes
[72.] Chen et al (2018)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[73.] Cheung et al (2013)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[74.] Chu et al (2018)	Low	Moderate	Moderate	High	Moderate	Moderate	Moderate	Low	Moderate	Yes
[75.] Chudasama et al (2019)	Moderate	Moderate	Low	High	Moderate	Low	Moderate	Low	Moderate	Yes
[76.] Cimarras-Otal et al (2014)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[77.] Chin et al (2016)	Moderate	Moderate	Moderate	High	Moderate	Low	Moderate	Low	Moderate	Yes
[78.] Agrawal et al (2016)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[79.] Gu et al (2018)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[80.] Gunn et al (2012)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[81.] Han et al (2013)	High	High	Moderate	High	Moderate	High	Moderate	Unclear	High	No
[82.] Hanlon et al (2018)	Low	Moderate	Moderate	High	Low	Low	Moderate	Low	Low	Yes
[83.] Jantsch et al (2018)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes

Author	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Publication bias	Conflict of interest	Overall rating	Reporting of MM measure and definition
[84.] John et al (2003)	Moderate	High	Moderate	High	Low	High	Moderate	Low	High	No
[85.] Johnson-Lawrence et al (2017)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[86.] Johnston et al (2019)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	No
[87.] Jones et al (2016)	Low	Moderate	Moderate	High	Low	Low	Moderate	Unclear	Moderate	Yes
[88.] Jovic et al (2016)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[89.] Juul-Larsen et al (2020)	High	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[90.] Hudon et al (2008)	Low	Moderate	Moderate	High	Low	Low	Moderate	Low	Low	Yes
[91.] Hussain et al (2015)	Moderate	Moderate	High	High	Moderate	Low	Moderate	Low	Moderate	Yes
[92.] Ie et al (2017)	High	High	Moderate	High	Moderate	Low	Moderate	Low	High	Yes
[93.] Ishizaki et al (2019)	Moderate	Moderate	Low	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[94.] Danon-Hersch et al (2012)	Moderate	High	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[95.] de Heer et al (2013)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[96.] Demirchyan et al (2013)	High	Moderate	Low	High	Moderate	High	Moderate	Low	High	No
[97.] Fabbri et al (2015)	Moderate	Moderate	High	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[98.] Fillenbaum et al (2000)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes

Author	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Publication bias	Conflict of interest	Overall rating	Reporting of MM measure and definition
[99.] Kaneko et al (2019)	Moderate	Moderate	High	High	Moderate	Low	Moderate	Low	Moderate	No
[100.] Kang et al (2017)	High	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[101.] Gandhi et al (2020)	Moderate	Moderate	Moderate	High	High	High	Moderate	Low	Moderate	Yes
[102.] Costa et al (2018)	High	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[103.] Rizzuto et al (2017)	High	Moderate	High	High	Moderate	Moderate	Moderate	Low	Moderate	Yes
[104.] Dhalwani et al (2017)	Moderate	Moderate	Low	High	Moderate	High	Moderate	Low	Moderate	Yes
[105.] Elixhauser et al (1998)	Low	Moderate	High	High	Low	Low	Moderate	Unclear	Low	Yes
[106.] Fabbri et al (2015)	High	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[107.] Fortin et al (2014)	Low	Moderate	Low	High	Moderate	Moderate	Moderate	Low	Moderate	Yes
[108.] Fuchs et al (1998)	Moderate	Moderate	Moderate	High	Moderate	Low	Moderate	Unclear	Moderate	No
[109.] Galenkamp et al (2011)	Low	Moderate	High	High	Moderate	High	Moderate	Unclear	High	No
[110.] Galenkamp et al (2016)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[111.] Gamma et al (2001)	High	Moderate	High	High	Moderate	High	Moderate	Unclear	High	No
[112.] Ge et al (2018)	Moderate	Moderate	High	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[113.] Ge et al (2019)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes

Author	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Publication bias	Conflict of interest	Overall rating	Reporting of MM measure and definition
[114.] Gould et al (2016)	Moderate	Moderate	Moderate	High	High	High	Moderate	Unclear	Moderate	Yes
[115.] Habib et al (2014)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	No
[116.] Harrison et al (2017)	Low	Moderate	High	High	Moderate	Low	Moderate	Unclear	Moderate	No
[117.] Hayek et al (2017)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[118.] Henninger et al (2012)	Moderate	Moderate	High	High	Moderate	High	Moderate	Unclear	Moderate	No
[119.] Hernandez et al (2019)	Moderate	Moderate	Moderate	High	High	High	Moderate	Unclear	Moderate	Yes
[120.] Ho et al (2014)	Moderate	Moderate	High	High	Low	Low	Moderate	Low	Moderate	Yes
[121.] Khan et al (2019)	Low	Moderate	Low	High	Low	High	Moderate	Low	Low	Yes
[122.] Kiliari et al (2013)	High	Moderate	High	High	Moderate	Moderate	Moderate	Low	Moderate	No
[123.] King et al (2018)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[124.] Kingston et al (2018)	Low	Moderate	High	High	Moderate	High	Moderate	Unclear	High	Yes
[125.] Koyanagi et al (2018)	Low	Moderate	Moderate	High	Moderate	Low	High	Low	Moderate	Yes
[126.] Kriegsman et al (2004)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[127.] Kristensen et al (2019)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[128.] Kristensen et al (2019)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes

Author	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Publication bias	Conflict of interest	Overall rating	Reporting of MM measure and definition
[129.] Kunna et al (2017)	Low	Moderate	Low	High	Moderate	Low	High	Low	Low	Yes
[130.] Kuwornu et al (2014)	Moderate	Moderate	High	High	Moderate	Low	Moderate	Low	Moderate	Yes
[131.] Lai et al (2019)	Low	Moderate	High	High	Moderate	Low	Moderate	Low	Moderate	Yes
[132.] Lai et al (2018)	High	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[133.] Laires et al (2019)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[134.] Lang et al (2015)	Moderate	Moderate	Moderate	High	Moderate	Moderate	Moderate	Low	Moderate	Yes
[135.] Le Cossec et al (2016)	Low	Moderate	Moderate	High	Moderate	Moderate	Moderate	Low	Moderate	Yes
[136.] Lee et al (2007)	Low	Moderate	High	High	Low	Low	Moderate	Low	Low	Yes
[137.] Lee et al (2018)	Low	Moderate	High	High	High	Low	Moderate	Unclear	High	No
[138.] Li et al (2016)	Low	Low	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[139.] Li et al (2019)	Low	Moderate	Low	High	Moderate	Moderate	Moderate	Low	Moderate	No
[140.] Lujic et al (2017)	Low	Moderate	Moderate	High	Low	High	Moderate	Low	Moderate	Yes
[141.] LupianezUnclearVillanueva et al (2018)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[142.] Zhou et al (2018)	Moderate	Moderate	Moderate	High	Moderate	Low	High	Low	Moderate	Yes
[143.] Zhang et al (2019)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes

Author	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Publication bias	Conflict of interest	Overall rating	Reporting of MM measure and definition
[144.] Wong et al (2010)	High	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[145.] Weimann et al (2016)	Low	Moderate	Low	High	Moderate	High	Moderate	Low	Moderate	Yes
[146.] Wang et al (2017)	Low	Moderate	Low	High	Moderate	High	Moderate	Low	Moderate	Yes
[147.] Wang et al (2019)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	No
[148.] Wade et al (2019)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[149.] Maciejewski et al (2019)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[150.] Marengoni et al (2016)	Moderate	Moderate	High	High	Moderate	High	Moderate	Low	Moderate	Yes
[151.] Marengoni et al (2009)	Moderate	Moderate	High	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[152.] Marques et al (2018)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[153.] Mavaddat et al (2014)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[154.] McDaid et al (2013)	Low	Moderate	High	High	Moderate	High	Moderate	Low	High	Yes
[155.] Melis et al (2014)	High	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[156.] Min et al (2007)	High	Moderate	High	High	Moderate	High	Moderate	Unclear	High	Yes
[157.] Momtaz et al (2010)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[158.] Mondor et al (2018)	Low	Moderate	Low	High	Moderate	High	Moderate	Low	Moderate	Yes

Author	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Publication bias	Conflict of interest	Overall rating	Reporting of MM measure and definition
[159.] Muggah et al (2012)	Low	Moderate	High	High	Moderate	Low	Moderate	Low	Moderate	No
[160.] Nagel et al (2008)	Low	Moderate	Low	High	Moderate	High	Moderate	Low	Moderate	Yes
[161.] Niedzwiedz et al (2019)	Moderate	Moderate	High	High	Moderate	Low	Moderate	Unclear	Moderate	Yes
[162.] Nunes et al (2016)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[163.] Nunes et al (2017)	Low	Moderate	Moderate	High	Low	High	Moderate	Low	Moderate	Yes
[164.] Nunes et al (2015)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[165.] Olaya et al (2017)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[166.] Olivares et al (2017)	High	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	No
[167.] Park et al (2018)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	No
[168.] Patel et al (2006)	Moderate	Moderate	High	High	Moderate	High	Moderate	Unclear	Moderate	No
[169.] Pati et al (2016)	High	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[170.] Pati et al (2019)	Moderate	Moderate	Moderate	High	Moderate	Moderate	Moderate	Low	Moderate	Yes
[171.] Payne et al (2013)	Low	Moderate	Moderate	High	Moderate	Low	Moderate	Unclear	Moderate	Yes
[172.] Perez et al (2020)	Moderate	Moderate	Moderate	High	Moderate	Moderate	Moderate	Low	Moderate	Yes
[173.] Petersen et al (2019)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	No

Author	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Publication bias	Conflict of interest	Overall rating	Reporting of MM measure and definition
[174.] Pfortmueller et al (2013)	Moderate	Moderate	High	High	High	High	Moderate	Unclear	High	No
[175.] Pressley et al (1999)	Low	Moderate	High	High	Moderate	Low	Moderate	Unclear	Moderate	No
[176.] Prior et al (2016)	Low	Moderate	Moderate	High	Moderate	Low	Moderate	Unclear	Moderate	Yes
[177.] Ribeiro et al (2018)	High	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[178.] Ruel et al (2014)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[179.] Ruel et al (2014)	Moderate	Moderate	Moderate	High	Low	High	Moderate	Low	Moderate	Yes
[180.] Ryan et al (2018)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[181.] Schmidt et al (2016)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[182.] Schottker et al (2016)	Moderate	Moderate	Moderate	High	Moderate	Moderate	Moderate	Low	Moderate	Yes
[183.] Seo et al (2017)	Low	Moderate	Moderate	High	Low	High	Moderate	Low	Moderate	No
[184.] She et al (2019)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[185.] Singh et al (2019)	Low	Moderate	Moderate	High	Low	Low	Moderate	Unclear	Moderate	Yes
[186.] Stepanova et al (2015)	Low	High	High	High	High	High	High	Unclear	High	Yes
[187.] Stickley et al (2020)	Low	Moderate	High	High	Moderate	High	Moderate	Low	High	Yes
[188.] Streit et al (2014)	Moderate	Moderate	Moderate	High	High	High	Moderate	Unclear	Moderate	Yes

Author	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Publication bias	Conflict of interest	Overall rating	Reporting of MM measure and definition
[189.] Stubbs et al (2018)	Low	Moderate	High	High	Moderate	Low	Moderate	Low	Moderate	Yes
[190.] Su et al (2016)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[191.] Sundstrup et al (2017)	Low	Moderate	High	High	Moderate	High	Moderate	Unclear	High	Yes
[192.] Takahashi et al (2016)	Moderate	Moderate	High	High	High	Low	Moderate	Low	High	No
[193.] Tinetti et al (2011)	Low	Moderate	High	High	High	High	Moderate	Unclear	High	No
[194.] Troelstra et al (2020)	High	Moderate	High	High	Moderate	Low	Moderate	Unclear	High	Yes
[195.] van Zon et al (2020)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[196.] Vancampfort et al (2017)	Low	Moderate	Moderate	High	Moderate	Low	Moderate	Low	Moderate	Yes
[197.] Vassilaki et al (2015)	Low	Moderate	Moderate	High	Moderate	Low	Moderate	Unclear	Moderate	Yes
[198.] Vassilaki et al (2016)	Low	Moderate	Moderate	High	Moderate	Low	Moderate	Unclear	Moderate	Yes
[199.] Villarreal et al (2015)	High	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	No
[200.] Violan et al (2019)	Low	Moderate	Moderate	High	High	Low	Moderate	Low	Moderate	Yes
[201.] von Strauss et al (2000)	Moderate	Moderate	Moderate	High	Moderate	Low	Moderate	Low	Moderate	No
[202.] Vos et al (2013)	Moderate	Moderate	High	High	Moderate	High	Moderate	Low	Moderate	No
[203.] Vu et al (2019)	High	Moderate	High	High	Moderate	High	Moderate	Low	High	No

Author	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Publication bias	Conflict of interest	Overall rating	Reporting of MM measure and definition
[204.] Wang et al (2018)	Moderate	Moderate	Low	High	Moderate	Low	Moderate	Unclear	Moderate	Yes
[205.] Wang et al (2017)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[206.] Wijers et al (2019)	Low	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	No
[207.] Williams et al (2016)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	No
[208.] Woldesemayat et al (2018)	High	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[209.] Yao et al (2020)	Moderate	Moderate	Low	High	Moderate	High	Moderate	Low	Moderate	Yes
[210.] Yorke et al (2017)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[211.] You et al (2019)	Moderate	Moderate	Moderate	High	Moderate	High	Moderate	Low	Moderate	Yes
[212.] Zhang et al (2020)	Moderate	Moderate	Low	High	Moderate	Low	Moderate	Low	Moderate	Yes
[213.] Khanam et al (2011)	Moderate	Moderate	Moderate	High	Moderate	Low	Moderate	Unclear	Moderate	Yes
[214.] Cornell et al (2009)	Low	Moderate	High	High	Moderate	Low	Moderate	Unclear	Moderate	Yes
[215.] Cassell et al (2018)	Low	Moderate	High	High	Moderate	Moderate	Moderate	Low	Moderate	No
[216.] Wong et al (2019)	High	Moderate	Moderate	High	Moderate	High	Moderate	Unclear	Moderate	Yes
[217.] Puth et al (2017)	Moderate	Moderate	Moderate	High	Moderate	Moderate	Moderate	Low	Moderate	Yes

Table S7: Output of adjusted meta-analytic model based on 217 studies

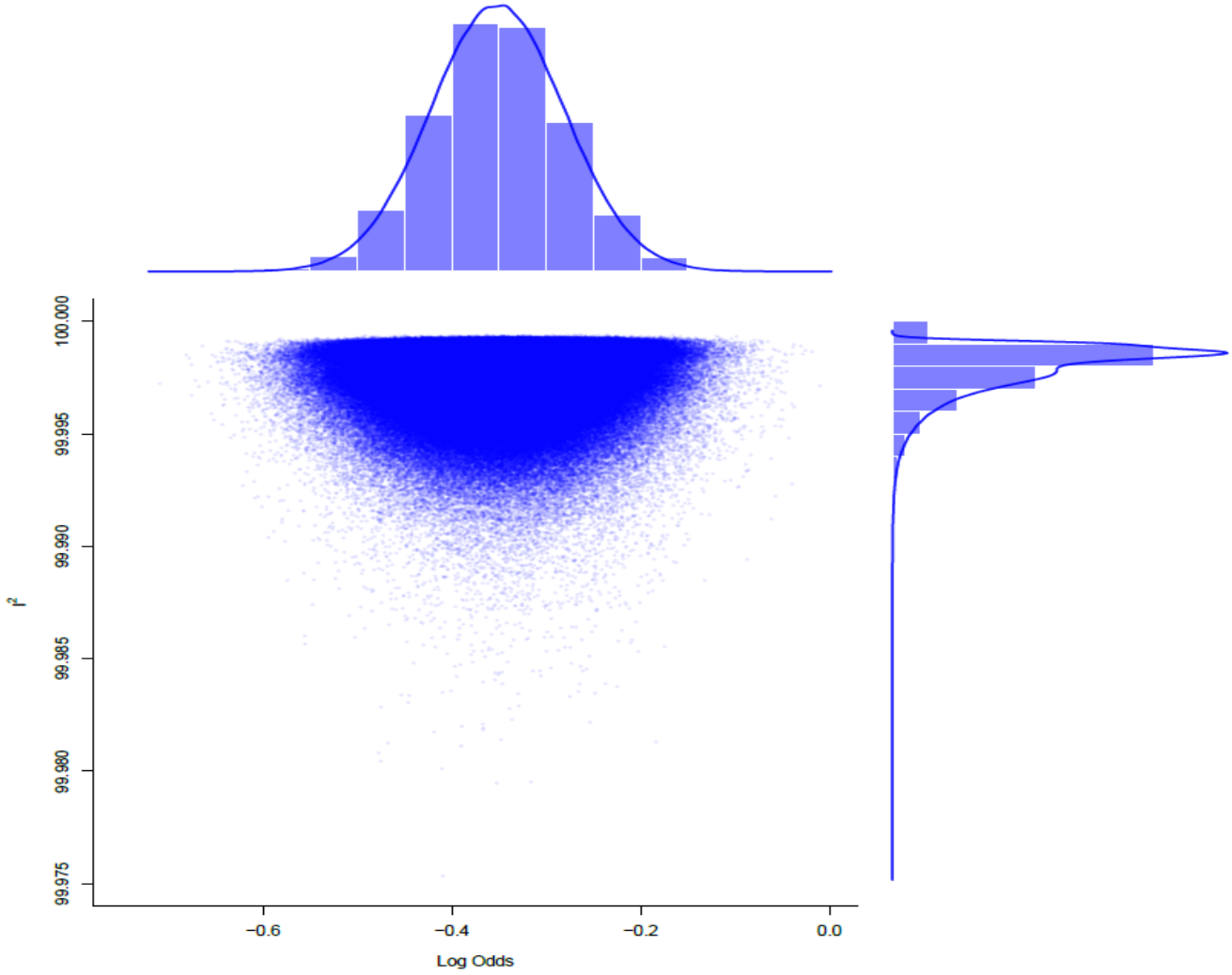
	Pooled prevalence of multimorbidity of each subgroup (%, 95% CI)	**Meta-regression Unadjusted Odds Ratio (95% CI)**	**Meta-regression Adjusted Odds Ratio (95% CI) R^2 42.4%**	**FMI**
Group of mean age		R^2 27.0%		
<59	30.4 (27.0-33.9)	Ref	Ref	Ref
59-73	43.5 (38.0-49.1)	1.8 (1.3-2.3)***	2.0 (1.6-2.6)***	0.3
≥74	67.8 (61.3-73.7)	6.4 (4.6-8.9)***	4.7 (3.4-6.5)***	0.2
No of conditions		R^2 6.9%		
<9	29.9 (24.9-35.4)	Ref	Ref	Ref
9-19	43.5 (39.1-47.9)	1.8 (1.3-2.5)***	1.7 (1.3-2.2)***	0.1
20-43	46.7 (38.4-55.2)	2.1 (1.4-3.1)***	2.2 (1.5-3.3)***	0.2
≥44	54.5 (32.6-74.8)	2.8 (1.5-5.4)**	2.8 (1.6-4.8)***	0.1
Setting		R^2 3.7%		
Community	37.8 (34.4-41.4)	Ref	Ref	Ref
Primary care	51.2 (41.6-60.7)	1.7 (1.2-2.5)**	1.8 (1.2-2.6)**	0.1
Hospital	47.1 (31.9-63.0)	1.5 (0.9-2.4)	0.8 (0.5-1.3)	0.1
Care home	73.9 (72.8-74.9)	4.6 (0.6-36.6)	1.5 (0.3-8.4)	0.04
Source		R^2 2.8%		
Self-report	38.3 (34.4-42.2)	Ref	Ref	Ref
Database	48.9 (42.2-55.6)	1.5 (1.1-2.1)**	0.8 (0.6-1.1)	0.1
Continent		R^2 7.4%		
North America	48.9 (42.1-55.7)	Ref	Ref	Ref
Europe	44.0 (37.7-50.4)	0.8 (0.6-1.2)	0.5 (0.4-0.7)***	0.1
Australasia	28.2 (20.3-37.6)	0.4 (0.2-0.8)**	0.4 (0.2-0.6)***	0.08
Asia	34.3 (28.6-40.5)	0.5 (0.4-0.8)**	0.5 (0.3-0.7)***	0.1
South America	47.5 (31.2-64.4)	0.9 (0.5-1.8)	0.8 (0.5-1.3)	0.1
Africa	13.8 (4.5-35.2)	0.2 (0.06-0.5)***	0.2 (0.1-0.5)***	0.1
Multiple continents	41.4 (31.0-52.6)	0.7 (0.4-1.4)	0.7 (0.4-1.2)	0.1

*<0.05 **<0.01 ***<0.001
Ref: Reference category. FMI: Fraction of missing information.

Table S8: Definition of variables

Variable name	Definition
Study setting	
Community	Studies that used population surveys, insurance claims databases, or research databases
Primary care	Studies that were carried out in primary care settings
Hospital	Studies that were carried out in hospital settings
Data source	
Self-report	Studies that collected data using self-report or interviews
Medical records and administrative databases	Studies that collected data using electronic medical records, medical chart reviews, insurance claims databases, pharmacy databases, or research databases
Study population	
All adults	Studies with a sample of population aged 18 and older (n=45), aged 20 and older (n=8), aged 21 and older (n=3), aged 25 and older (n=2), or others (n=27) (e.g. aged 16 and older, or aged 17 and older)
Middle-aged and older	Studies with a sample of population aged 50 and older (n=25), aged 40 and older (n=5), aged 40 and older (n=10), or others (n=6) (e.g. aged 57 and older, or aged 45 and older)
Only older people	Studies with a sample of population aged 65 and older (n=22), aged 60 and older (n=25), aged 70 and older (n=5) or others (n=11) (e.g. aged 68 and older, aged 77 and older, aged 78 and older, or aged 80 and older)

Figure S1: Graphical display of study effect sizes and heterogeneity



No obvious subgroup effects were identified

Figure S2: Process of examining and identifying outlying studies in meta-analysis

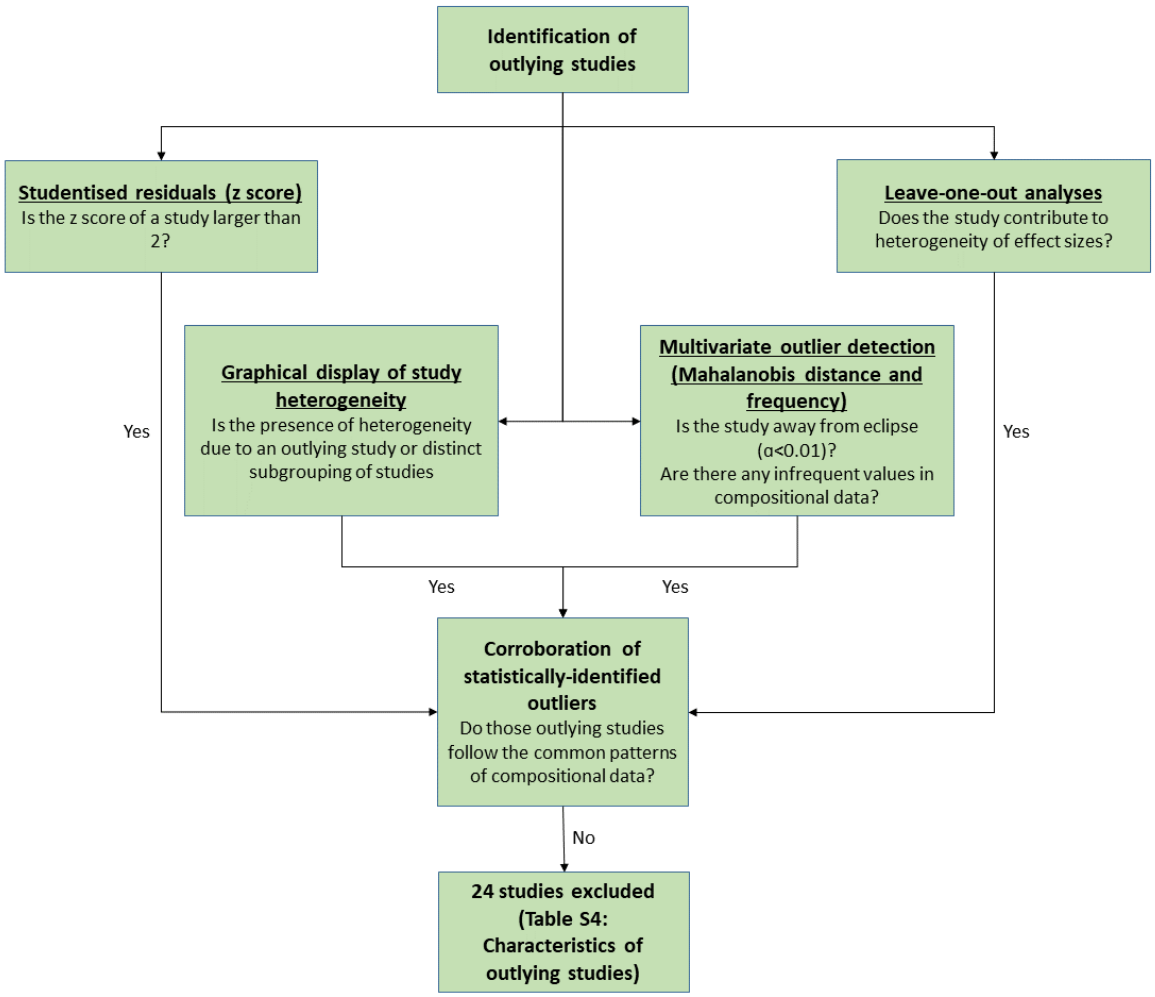


Figure S3: Summary of risk of bias assessment

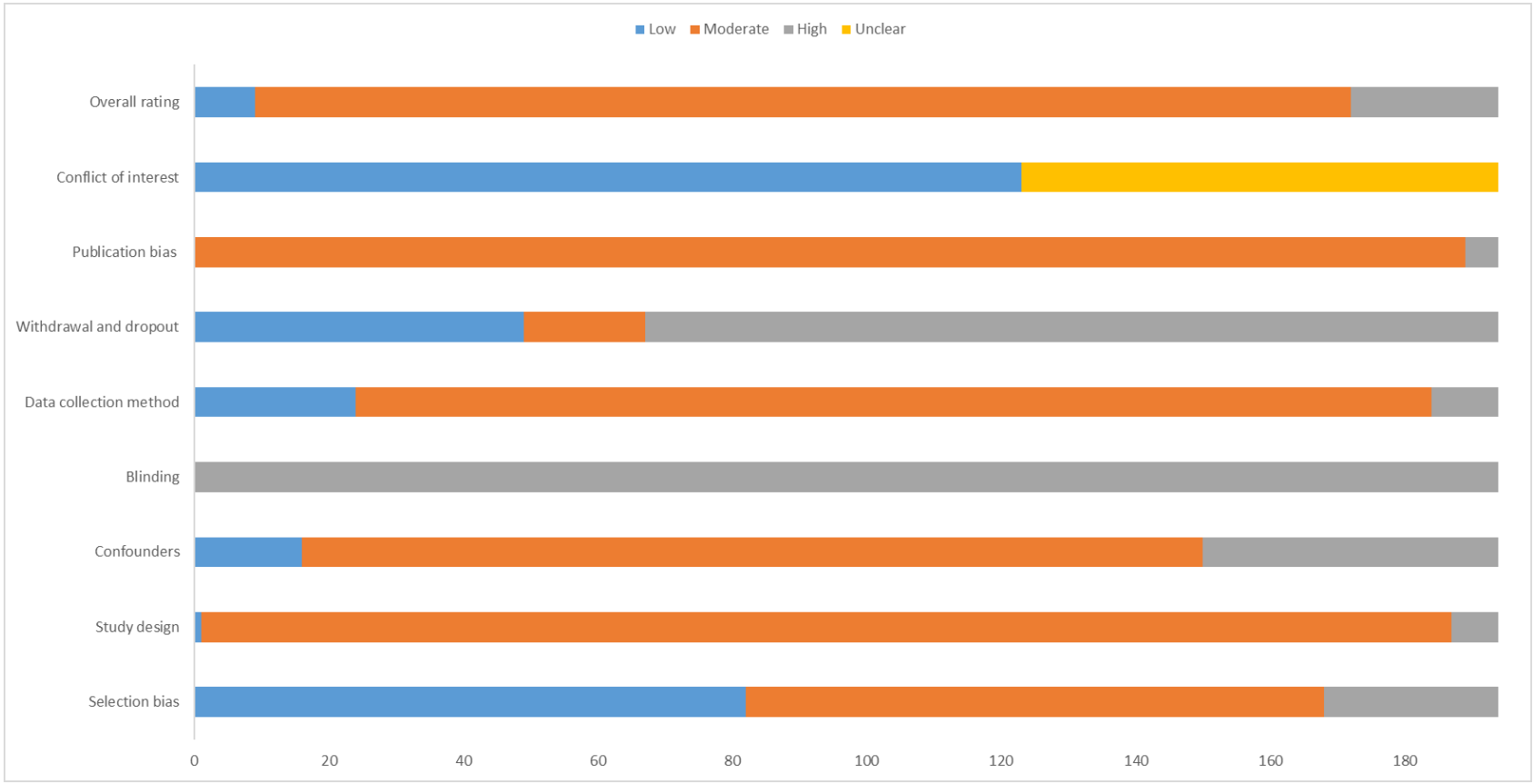
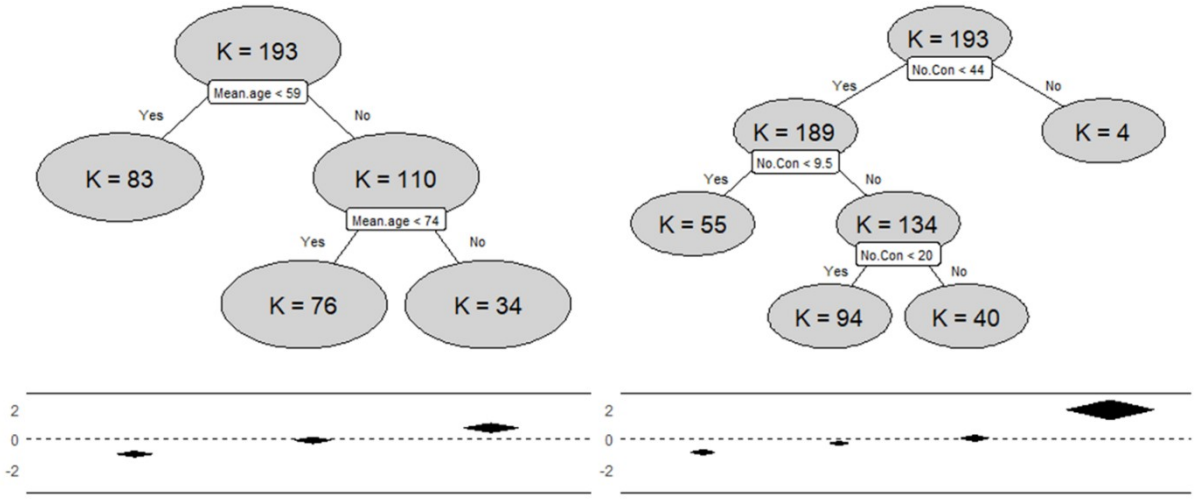


Figure S4: Meta-regression trees for predicting the pooled estimated prevalence of multimorbidity (based on 'mean age' and 'number of conditions' predictors. unit: log(odds))



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PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Table S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 6, Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Supplementary Table S8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 6 Supplementary p26
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 7-8

| Section/topic | # | Checklist item | Reported on page # |

PRISMA Checklist

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 10 and Table 2
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 7-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 8-9, Table 1; Supplementary Table S4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary Table S6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 9-10 Figure 2-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 9-10 Table 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 9-10, Table 1 and Table 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 10-11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 11,12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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